From Singing to Speaking: Using Melodic Intonation Therapy to Facilitate Language Recovery in Patients with Non-fluent Aphasia

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“If the human brain were so simple
That we could understand it,
We would be so simple
That we couldn’t.”

Emerson M. Pugh

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Table of Contents

List of abbreviations

AAC	Alternative and Augmentative Communication
ADC	Apparent Diffusion Coefficient
AF	Arcuate Fasciculus
AAT	Aachen Aphasia Test
BA	Brodmann Area
BDAE	Boston Diagnostic Aphasia Examination
BNT	Boston Naming Test
BOLD	Blood Oxygenation Level Dependent
CAT	Computer Assisted Treatment
CIAT	Constrained Induced Aphasia Therapy
CILT	Constrained Induced Language Therapy
CIMT	Constraint Induced Movement Therapy
CIU	Correct Information Unit
COT	Computer Only Treatment
CSF	Corticospinal Fluid
CST	Corticospinal Tract
CT	Computed Tomography
CVA	Cerebrovascular Accident
DTI	Diffusion Tension Imaging
DWI	Diffusion Weighted Imaging
EPI	Echo Planar Imaging
EmC	Extreme Capsule Fibers
FA	Fractional Anisotropy
FDR	False Discovery Rate
FIR	Finite Impulse Response
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	functional Magnetic Resonance Imaging
FOV	Field Of View
FWE	Family Wise Error
FWHM	Full Width at Half Maximum
GLM	General Linear Model
GM	Grey Matter
GUI	Graphical User Interface
HRF	Hemodynamic Response Function

IFG	Inferior Frontal Gyrus
IRB	Institutional Review Board
ISI	Interstimulus Interval
MCA	Middle Cerebral Artery
MDM	Magnetic Dipole Moment
MEG	Magnet Encephalography
MIT	Melodic Intonation Therapy
µm	Micrometer
mm^3	Cubic millimeter
MNI	Montreal Neurological Institute
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MTG	Middle Temporal Gyrus
NMR	Nuclear Magnetic Resonance
PCG	Precentral Gyrus
PET	Positron Emission Tomography
PLIC	Posterior Limb Internal Capsule
RA	Relative Anisotropy
RCPM	Raven's Colored Progressive Matrices
RF	Radio Frequency
ROI	Region Of Interest
SLF	Superior Longitudinal Fasciculus
SNR	Signal-to-Noise Ratio
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SRT	Speech Repetition Therapy
STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
TA	Acquisition Time
tDCS	transcranial Direct Current Stimulation
TIA	Transient Ischemic Attack
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TR	Repetition Time
UF	Uncinate Fasciculus
VLSM	Voxelbased Lesion Symptom Mapping
WM	White Matter

Summary

Aphasia is a common and devastating complication of stroke or other brain injuries that results in the loss of ability to produce and/or comprehend language. It has been estimated that 24-52% of acute stroke patients have some form of aphasia if tested within 7 days of their stroke; 12% of survivors still have significant aphasia at 6 months after stroke (Wade et al., 1986). At present there are no universally accepted methods or 'gold-standards' for the treatment of severe nonfluent aphasia and most interventions administered in the subacute and chronic stroke phase are tailored to the patient's individual impairment profile. *Melodic Intonation Therapy (MIT)* is a treatment approach for non-fluent aphasic patients which was specifically developed after the observation that patients with severe nonfluent aphasia are better in singing lyrics than they are at speaking the same words. The two unique elements which set MIT apart from other, non-intonation-based therapies are the melodic intonation (singing) with its inherent continuous voicing, and the rhythmic tapping of each syllable – using the patient's left hand – while phrases are intoned and repeated, serving as a catalyst of fluency.

The 4 studies presented in this dissertation aimed at investigating the efficacy of MIT in an open-label pilot clinical trial. Patient's language abilities were assessed at 5 different timepoints during the course of an intensive 15-week therapy in order to evaluate improvements in propositional speech and possible effects of generalization to unpracticed words and phrases. Functional magnetic resonance imaging (fMRI) was used in order to determine the neural treatment effect and the reorganization/plastic changes in the brain. Large left hemisphere lesions which extend into the deep white matter left most of the patients with partially or fully damaged white matter fiber tracts which belong to the language network. We hypothesized that this loss would be compensated for by the language network on the right hemisphere. Using diffusion tensor imaging (DTI), changes in the structure of the white matter on the right hemisphere comparing pre with post therapy were investigated. Furthermore we created a new variable "lesionload", which combines the lesionmaps of patients with canonical fiber tracts derived from healthy subjects in order to assess the extent of the damage and to predict speech outcome.

Study 1 with the title *"From singing to speaking: Why singing may lead to recovery of expressive language function in patients with Broca's aphasia"* investigated the unique and shared elements of MIT and aimed to contrast its behavioral and neural treatment effects with a control intervention called Speech Repetition Therapy (SRT). SRT is identical to MIT ex-

cept that the phrases were spoken rather than intoned (sung), syllables were not sustained, and there was no hand tapping associated with the production of speech. Two prototypical patients with similar impairments and stroke size/location were treated for the same amount of time (1.5 hours/day, 5 days/week). Both interventions' post-treatment outcomes revealed significant improvement in propositional speech that generalized to unpracticed words and phrases; however, the MIT-treated patient's gains surpassed those of the control-treated patient. Treatment-associated imaging changes indicate that MIT's unique engagement of the right hemisphere, both through singing and tapping with the left hand to prime the sensorimotor and premotor cortices for articulation, accounts for its effect over non-intoned speech therapy. *(Schlaug, G., Marchina, S., & Norton, A., 2008. Music Perception, 25, 4:315-323.)*

Study 2, entitled *"From singing to speaking: behavioral and neural correlates of intensive treatment with Melodic Intonation Therapy,"* aimed to investigate the behavioral and neural correlates of intensive MIT in an open-label-proof-of-concept trial in a group of 14 chronic stroke patients (>1 year after their stroke) with moderate to severe non-fluent aphasia and relatively unimpaired comprehension. In this study, we compared pre-treatment assessments to determine the stability of baseline impairments with multiple interim (after 75 sessions) and post-treatment assessments (1 month after therapy) to assess any improvement in speech output from a stable baseline and to relate this improvement to functional imaging changes. We found significant improvements in a measure of propositional speech and found evidence that the improvement generalized to unpracticed words and phrases. Baseline variations prior to therapy were minimal and repeat post-treatment assessments showed that this group of chronic non-fluent aphasic patients maintained their speech output improvement. Treatment-associated imaging changes were seen in a right-hemisphere network that included the superior temporal gyrus, the primary sensorimotor, premotor, and posterior inferior frontal cortex, the pre-supplementary motor region, and the supramarginal gyrus, most regions connected via the arcuate fasciculus. Of all those regions, only imaging changes in the posterior IFG region are correlated with improvements in speech output. Our data suggest that MIT can lead to persistent gains in speech output in chronic non-fluent patients, and that changes in a right-hemispheric network of brain regions, in particular in the right posterior IFG are related to the improvements.
(Marchina, S., Norton, A., & Schlaug, G., submitted to Brain)

In **study 3** with the title **"***Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy"* we investigated whether intensive MIT in chronic non-fluent aphasic patients with relatively large left-hemisphere lesions would not only lead to functional changes in the brain as reported previously, but would also change white matter structure of the brain. The critical white matter fiber tract that facilitates both speech production and its feedforward and feedback control system is the arcuate fasciculus (AF). Using DTI streamline fiber tracking, we examined 6 patients' arcuate fasciculus of the undamaged right hemisphere pre and post MIT. The results revealed a significant increase in number of AF fibers and AF volume post compared to pre treatment. The correlation between change in AF and post versus pre behavioral changes didn't reach significance, however a strong trend was observed. This white matter changes indicate a remodeling of the AF due to a need for stronger, more effective connections between speech-relevant brain regions in the right hemisphere.
(Schlaug, G., Marchina, S., & Norton, A., 2009. Ann. N.Y.Acad.Sci., 1169:385-394.)

In **study 4**, entitled **"***Impairment of speech production predicted by lesion load of the left arcuate fasciculus,"* we quantitatively examined the relationship between lesion size, language tract involvement, and impairment of speech production. The lesion maps of 30 chronic stroke patients were overlaid with probabilistic maps of the arcuate fasciculus (AF), uncinate fasciculus (UF), and the extreme capsule (EmC) fiber system, which were derived from diffusion tensor images of healthy, age matched subjects. We then used lesion load – the volume of a particular tract affected by a patient's lesion – of these tracts to predict three different measures of speech production (rate, accuracy and overall efficiency). Regression analyses showed that AF-lesion load, but not EmC- or UF-lesion load or lesion size, significantly predicted performance of the three examined speech measurements. This new variable, AF-lesion load, not only complements established voxel-based lesion mapping techniques, but moreover may be potentially be used to estimate impairment and recovery potential after stroke and refine inclusion criteria for experimental rehabilitation programs.
(Marchina, S., Zhu, L.L., Norton, A., Zipse, L., Wan, C.Y., & Schlaug, G., 2011. Stroke, 42:2251-56.)

Zusammenfassung

Aphasie ist eine schwerwiegende Störung der menschlichen Sprachproduktion und Sprachverarbeitung, die häufig nach einem Schlaganfall oder einer Hirnverletzung auftritt. Schätzungen zufolge weisen 24-52% der akuten, innerhalb von 7 Tagen nach einem Schlaganfall getesten Patienten eine gewisse Form von Aphasie auf. Jeder achte, der einen Schlaganfall überlebt, zeigt selbst nach 6 Monaten noch signifikante Symptome einer Aphasie (Wade et al., 1986). Dennoch gibt es gegenwärtig keine universell akzeptierte Methode oder einen Goldstandard für die Behandlung von schweren nicht-flüssigen Aphasien. Die meisten in der subakuten und chronischen Phase angewendeten Interventionen sind auf die individuellen Bedürfnisse und das Schädigungsprofil des jeweiligen Patienten massgeschneidert. Die *Melodic Intonation Therapy (MIT)* ist dagegen ein Behandlungsansatz (für non-fluent Aphasiker), der entwickelt wurde, nachdem beobachtet worden war, dass Patienten mit einer schweren non-fluent Aphasie besser darin sind, einen Liedtext zu singen als die entsprechenden Worte zu sprechen. Die zwei charakteristischen Elemente, welche die MIT von anderen nicht intonationsbasierten Therapien unterscheiden, sind 1.) die melodische Intonation (Singen) mit der inhärenten, kontinuierlichen Stimmgebung und 2.) das rhythmische Klopfen jeder Silbe mit der linken Hand, während der Patient die Phrasen intoniert und repetiert. Die beiden Elemente dienen als Katalysator für eine Verbesserung der Sprechflüssigkeit.

Die 4 Studien, die in der vorliegenden Doktorarbeit präsentiert werden, verfolgen das gemeinsame Ziel, die Wirksamkeit der MIT in einer offenen, nicht verblindeten klinischen Studie zu untersuchen. Die sprachlichen Funktionen der Patienten wurden im Zeitraum einer intensiven 15-wöchigen Therapie zu verschiedenen Zeitpunkten getestet, um die Verbesserung in der Spontansprache sowie mögliche Effekte der Generalisierung auf nicht geübte Wörter und Phrasen zu evaluieren. Mittels funktioneller Bildgebung wurden die neuronalen Behandlungseffekte und die Reorganisation/plastischen Veränderungen im Gehirn eruiert und festgehalten. Die meisten Patienten wiesen grosse Läsionen in der linken Hemisphäre auf, die tief in die weisse Substanz reichen und dort mit teilweise oder komplett geschädigten Faserstrukturen einhergehen, die einem grösseren Sprachnetzwerk angehören. Wir hatten die Hypothese, dass dieser Verlust auf der linken Seite des Gehirns vom Sprachnetzwerk der rechten Hirnhälfte kompensiert würde. Mittels Diffusions-Tensor-Bildgebung (DTI) untersuchten wir deshalb die strukturellen Veränderungen der weissen Substanz in der rechten Hemisphäre, die sich bei einem Vergleich von Post- mit Prä-Therapie ergeben. Darüber hinaus haben wir eine neue Variable „Lesionload“ kreiert, indem wir die individuellen Läsionskarten (lesion maps) der

Patienten mit der kanonischen Faserbahn von einer Gruppe gesunder Kontrollpersonen kombinierten. Mit dieser Variable versuchen wir nun, das Ausmass der Schädigung einzuschätzen sowie eine Prognose über die zukünftigen sprachlichen Funktionen des Patienten zu machen.

In **Studie 1** mit dem Titel *"From singing to speaking: Why singing may lead to recovery of expressive language function in patients with Broca's aphasia"* werden die charakteristischen Elemente sowie die verhaltensmässigen und neuronalen Behandlungseffekte der MIT mit jenen einer Kontrollintervention, der Speech Repetition Therapy (SRT), verglichen. SRT und MIT sind über weite Strecken identisch, unterscheiden sich aber typischerweise darin, dass bei der SRT gesprochene anstatt gesungene Phrasen verwendet und die Silben nicht gehalten werden. Zudem wird bei der SRT das Klopfen mit der Hand während der Sprachproduktion weggelassen. Im Rahmen unserer Studie wurden zwei prototypische Patienten mit ähnlicher Schädigung und vergleichbarer Lokalisation und Grösse des Schlaganfalls im gleichen Zeitumfang (1.5 Stunden/Tag, 5 Tage/Woche) therapiert. Für beide Interventionen zeigte sich im Resultat nach der Therapie eine signifikante Verbesserung in der Spontansprache, welche auf ungeübte Wörter und Phrasen generalisiert werden konnte. Allerdings übertraf die Leistungssteigerung des mit MIT diejenige des mit SRT behandelten Patienten. Die behandlungsinduzierten Veränderungen, die mittels Bildgebung sichtbar gemacht werden konnten, deuten darauf hin, dass die durch das Singen und das Klopfen mit der linken Hand (zur Aktivierung des primären sensorisch-motorischen und des prämotorischen Kortex) bedingte Einflussnahme der rechten Hemisphäre für die besseren Effekte der MIT im Vergleich zu der nicht intonierten Sprech-Therapie verantwortlich ist.
(Schlaug, G., Marchina, S., & Norton, A., 2008. Music Perception, 25, 4:315-323.)

Im Rahmen der **2. Studie**, *"From singing to speaking: behavioral and neural correlates of intensive treatment with Melodic Intonation Therapy"*, wurden in einem offenen klinischen Trial/Experiment 14 chronische Schlaganfallpatienten mit persistenter non-fluent Aphasie, aber relativ gutem Sprachverständnis mehrmals vor, unmittelbar nach den 75 regulären MIT-Sitzungen und schliesslich 1 Monat nach Abschluss der Therapie untersucht. Die Messungen, die vor der MIT durchgeführt wurden und eine stabile Messbasis (Baseline) gewährleisten sollten, wurden mit den Messdaten nach der Therapie verglichen, um allfällige Verbesserungen der Sprechfähigkeit zu ermitteln und diese mit den funktionellen Veränderungen zu korrelieren. Der Vergleich der Prä-/Post-Therapie-Resultate zeigte erwartungsgemäss eine signifikante Verbesserung der Spontansprache und sogar eine Generalisierung auf nicht-trainierte

Wörter und Phrasen. Die vor der MIT erhobenen Baseline-Daten variierten nur minimal und in Assessments nach der Behandlung stellte sich heraus, dass die Patienten ihre verbesserte sprachliche Leistung selbst nach Beendigung der Therapie erhalten konnten. Die Messungen mittels Bildgebung (fMRI) ergaben verstärkte Aktivierungen in einem rechtshemisphärischen Netzwerk, bestehend aus Gyrus temporalis superior, primärem sensorisch-motorischem sowie prämotorischem Kortex, posterior inferiorer Frontalregion, pre-supplementorischem Areal und inferiorem Parietalkortex –, wobei die meisten dieser Regionen durch den Fasciculus Arcuatus verbunden sind. Von den gemessenen Aktivierungsunterschieden korrelierten allerdings nur jene im Gyrus frontalis inferior signifikant mit der Verbesserung in den sprachlichen Funktionen. Die Resultate weisen darauf hin, dass die MIT zu einer anhaltenden Verbesserung der Sprechfähigkeit bei chronischen non-fluent Patienten führen kann und dass die sprachlichen Verbesserungen mit Veränderungen in einem rechtshemisphärischen Netzwerk von Hirnregionen – vor allem dem Gyrus frontalis inferior – assoziiert sind.
(Marchina, S., Norton, A., & Schlaug, G., submitted to Brain.)

In **Studie 3** mit dem Titel **"***Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy"* wollten wir herausfinden, ob eine intensive MIT bei chronischen nicht-flüssigen Aphasie-Patienten mit relativ grossen Läsionen in der linken Hirnhälfte nebst den funktionellen Veränderungen im Gehirn (wie sie in der vorangehenden Studie 2 berichtet werden) auch die Struktur der weissen Substanz des Gehirns verändert. Jene Faserbahn in der weissen Substanz, welche sowohl die Sprachproduktion als auch dessen Feedforward- und Feedback-Kontroll-System ermöglicht, ist der Fasciculus Arcuatus (AF). Mit dem Einsatz von DTI-Traktographie haben wir bei 6 Patienten den AF in der unbeschädigten rechten Hemisphäre vor und nach der Therapie untersucht. Die Resultate des Prä-Post-Therapie-Vergleichs offenbaren einen signifikanten Anstieg von Fasern und Volumen des AF. Die Korrelation zwischen den Veränderungen im AF und jenen in den behavioralen Daten vor und nach der Therapie ist zwar statistisch nicht signifikant, zeigt jedoch einen starken Trend. Die Veränderungen in der weissen Substanz indizieren ein Umformen/Umorganisieren des AF als Folge davon, dass stärkere und effektivere Verbindungen zwischen den sprachrelevanten Regionen der rechten Hemisphäre benötigt werden.
(Schlaug, G., Marchina, S., & Norton, A., 2009. Ann. N.Y.Acad.Sci., 1169:385-394.)

In einer **4. Studie** wurde unter dem Titel ***"****Impairment of speech production predicted by lesion load of the left arcuate fasciculus"* die Beziehung zwischen Läsionsgrösse, Beteiligung des Sprachtrakts und Beeinträchtigung der Sprachproduktion quantitativ untersucht. Die individuellen Läsionskarten (lesion maps) von 30 chronischen Schlaganfallpatienten wurden jeweils mit den probabilistischen „Maps" der Fasersysteme des Fasciculus Arcuatus (AF), des Fasciculus Uncinatus (UF) und der Capsula Extrema (EmC) kombiniert. Diese Faserbahnen wurden mittels der DTI-Bilder von gesunden Versuchspersonen entsprechenden Alters erstellt. Für die Prognose von 3 verschiedenen Messungen von Sprachproduktion (Sprachfrequenz, Genauigkeit und Effizienz) berechneten wir den „Lesionload", d.h. das Volumen des jeweiligen Areals, das von der Läsion betroffen ist. Regressionsanalysen zeigen, dass der AF-Lesionload die Leistung der drei Sprachmessungen signifikant voraussagen kann, nicht so der UF- oder der EmC-Lesionload oder die Läsionsgrösse. Die neu entwickelte Variable AF-Lesionload komplementiert nicht nur etablierte Voxel-based-lesion-mapping (VLSM)-Techniken, sondern kann ausserdem dazu dienen, Beeinträchtigung und Erholungspotential nach einem Schlaganfall einzuschätzen und die Einschlusskritierien für experimentelle Rehabilitationsprogramme zu verfeinern.
(Marchina, S., Zhu, L.L., Norton, A., Zipse, L., Wan, C.Y., & Schlaug, G., 2011. Stroke, 42:2251-56.)

I Theoretical Part

1 Introduction

"The limits of my language mean the limits of my world."

Ludwig Wittgenstein

The capacity for language in the complex and multi-modal form, as we experience it every day, is unique and exclusively reserved to humans. No other creature has even close to the possibilities of such a complex communication (Rütsche and Meyer, 2010). Despite the apparent ease with which we use language, especially speech is undoubtedly one of our most complex cognitive and motor skills. The loss of this skill has a massive impact on the social and professional lives of those affected and makes us aware of the extent to which our society is centered on language and how much language contributes to the formation of social, psychosocial and cultural identity.

The most common cause for a loss of the ability to process language in the brain is a cerebrovascular accident or a stroke (Wade et al., 1986). At least one-fourth of all stroke survivors[1] experience language impairments known as *aphasia*, involving the ability to speak, write, and understand spoken and written language. While there is a good chance for patients to regain their function through spontaneous recovery, a substantial part ends up having permanent language deficits.

More interestingly, research shows that the recovery process can be enhanced and more successful if supported by appropriate therapies (Robey, 1994, 1998). One particular approach called *Melodic Intonation Therapy (MIT)* which was introduced in the 1970s after the observation was made that patients with aphasia are able to sing, but speak the words, has been considered to be one of the most promising therapies for the treatment of aphasia for already more than 3 decades. By using melodic aspects and left hand tapping MIT tries to facilitate the use of language by the non-dominant right hemisphere, and utilizes the potential to change and reorganize the brain through intense treatment. Thus, MIT can be seen as an illustrative example for what is characteristically referred to as "the plastic human brain" (Jancke, 2009b) which is currently one of the hottest topics in the neuroscientific community and beyond.

[1] According to the American Heart Association (www.americanheart.org) stroke is the third largest cause for death behind heart disease and cancer.

Regardless of its attractiveness and despite the lack of alternatives MIT could quite surprisingly not be established in the clinical work so far. This is due to the fact that there are still no studies which show clear evidence for efficacy and long-term treatment effects.

Therefore, it is a main objective of this thesis to attain a better understanding of the neural basis of MIT-induced remission of speech in non-fluent aphasia and to examine the influence of duration of treatment as well as review the long-term effects with follow-up examinations. The dissertation is structured into 3 main parts: A theoretical part I will present a brief introductory overview into the topic of aphasia, its treatment and neuroscientific applications and perspectives. It highlights Melodic Intonation Therapy (MIT) as a particular form of aphasia treatment and closes with a brief outline of the two main imaging methods used in the empirical part. In part II several empirical studies in the form of independent manuscripts are introduced. The concluding part III discusses the presented papers in a larger context and finally concludes with a practical outlook for future work.

2 Aphasia: an overview

First and foremost, aphasia is not a disease, but a symptom of brain damage. In general, aphasia is a neurological disorder caused by damage to the portions of the brain that are responsible for language. Due to its multimodal character, the occurring impairments affect the different components of the language system (phonology, lexicon, syntax and semantic). Primary signs of the disorder affect expressive and receptive language modalities which includes speaking, understanding of speech, and difficulty with reading and writing. The type and severity of language dysfunction depends on the precise location and extent of the damaged brain tissue.

Remarkably, studying and scrutinizing the phenomenon of aphasia since its beginning in the second half of the 19th century can be seen as the starting point and fundament of what we nowadays know about the language system. Before functional neuroimaging techniques became available, the only ways to study brain function were animal research and deficit-lesion studies. The intent of the latter is to relate the behavior of brain damaged patients to the observed site of the damage in a post-mortem analysis. With this approach assumptions about brain functions and their location in the brain could be made. Since language is a uniquely human capability, the history of the cognitive neuroscience of language is deeply rooted in deficit-lesion studies investigating aphasia.

2.1 Aphasia and our understanding of language

The classical view of hemispheric specialization of language organization within the cortex goes back to observations on patients who showed language deficits. Paul Broca and Karl Wernicke revealed in early studies of aphasia that damage of two distinct cortical regions – one in the lateral frontal (Broca's area) and the other in the posterior superior temporal lobe (Wernicke's area) – was associated with a linguistically different profile of language impairment. Broca's patient was not able to articulate language while Wernicke's patient had impaired speech comprehension. Beginning with these lesion studies, an early model of lateralized speech processing was developed based on the idea that language was localized in structures which are functionally and structurally interconnected to accomplish the brain's language system (Lichtheim, 1885). This model, referred to as the *classical localizationist view* was dominant through a long time of clinical research on aphasia. Jules Dejerine accepted basic ideas of Wernicke and Lichtheim and defined a zone of language in the early 1900s as that region of the left hemisphere responsible for language.[2] Norman Geschwind revived the Lichtheim Model in the 1960s and on the basis of the Wernicke-Lichtheim model developed his own model of language known today as the *Wernicke-Geschwind Model* (Geschwind, 1965a, b, 1970). This general model formed the basis for a useful classification of the aphasias and provided a framework for the investigation of the neural basis of language processes. However lesion studies and the advent of modern neuroimaging methods have shown that the neural organization of language is far more complex than this model suggests (Dronkers et al., 2000).

A more recent model of speech processing was proposed by Hickok and Poeppel (2004). Based on Wernicke's famous model of speech processing and the already well accepted dual-stream model in the visual domain, they outline a dual stream model of the functional anato-

[2] It is located within the distribution of the middle cerebral artery, surrounding the sylvian fissure on the lateral surface of the hemisphere, including portions of the frontal, parietal, and temporal lobes. The zone includes Broca on the anterior and Wernicke's area on the posterior. Subcortical white matter pathways, including the arcuate fasciculus and superior longitudinal fasciculus connect Broca and Wernicke's area. These white matter pathways pass through the angular gyrus and supramarginal gyrus at the posterior rim of the sylvian fissure in the temporo-parieto junction. Lesions in different parts of the zone of language may produce different aphasia syndromes. Although lesions in or near the zone of language typically produce predictable and characteristic clinical syndromes of aphasia, it would be a mistake to consider the zone of language as a "center" where all the language processes are located. It should rather be regarded as a critical component (major intersection) of several overlapping neural networks, widely distributed throughout the brain, whose total combined activity has the effect of producing language as we know. (cf. Helm-Estabrooks and Albert, 2004)

my of language (Hickok and Poeppel, 2004). In this model, a ventral stream processes speech signal for comprehension and a dorsal stream maps acoustic speech signals to frontal lobe articulatory networks. Furthermore it assumes that the ventral stream is largely bilaterally organized – although there are important computational differences between left- and right hemisphere systems – and that the dorsal stream is strongly left lateralized.

Unlike the early lesion-deficit studies which were mostly post-mortem examinations, more recent investigations rely on modern imaging methods as well as recently developed *voxel-based-lesion-symptom mapping techniques (VLSM*) to analyze the relationship between tissue damage and behavior on a voxel-by-voxel basis (Bates et al., 2003; Rorden et al., 2007). Different studies have utilized these technique in order to examine in stroke patients with aphasia which brain regions are related to various language functions such as verbal fluency (Baldo et al., 2006), speech production (Borovsky et al., 2007), naming (Parkinson et al., 2009; Piras and Marangolo, 2007) or comprehension (Dronkers and Ogar, 2004). For this thesis project I likewise used modern neuroimaging methods such as fMRI and DTI as well as a newly developed technique called *lesionload*.

2.2 Aphasia and its causes: stroke[3]

As it is known today aphasia can be caused by various accidents such as (traumatic) brain/head injury, seizure, tumors, infections or neurodegenerative disorders such as dementia or Parkinson. But aphasia is most commonly seen in adults who have suffered a cerebrovascular accident or stroke. There are two broad categories of stroke: 1.) *ischemic stroke* (80% of the cases) caused by a blockage or occlusion of blood flow that produces ischemia, i.e., the reduction of oxygen, and 2.) *hemorrhagic stroke* (20% of the cases) caused by a rupture of the blood vessel produces hemorrhage or bleeding into or around the brain.

2.2.1 Ischemic stroke

In a brain ischemia, the blood flow to part of the brain is cut off, and the cells in that region do not receive the oxygen and fuel (sugar) they need. The neurons stop functioning and die unless the blood flow is restored quickly. The cause for ischemia is mostly a blockage of an artery that brings oxygenated blood to some portion of the brain.

[3] Generally referring to Helm-Estabrooks and Albert (2004). In addition to this fundamental work on aphasia the following website is recommended: http://www.dana.org/news/brainhealth/detail.aspx?id=9824

- If the clot develops in the artery itself, the process is called *thrombosis*. This starts usually with plaques forming inside an artery due to atherosclerosis, or a hardening of the arterial walls. They grow in and under the inner lining of arteries and jut out into the space where blood should flow. Other vascular diseases can also narrow the artery, decreasing blood flow, but whatever the cause, narrowing of the artery impedes blood flow and causes a clot (thrombus) to form, perhaps completely clogging the artery.
- Alternatively, an artery can be blocked by material that originates elsewhere in the cardiovascular system and travels there. This process is called *embolism*. The material (an embolus) is usually a clot that originates in the heart, the aorta, or other blood vessels and then moves through the circulatory system. An embolus travels until it gets stuck in, and blocks, the first artery too small for it to pass through.

In any case, a brain damage caused by deprivation of blood is called *ischemic stroke*, the region of damage is called a *brain infarct*.

Since strokes can develop in any part of the circulatory system, they cause variable damages and loss of functions. Consequently, the symptoms of an ischemic stroke depend on the area of the brain that stops receiving blood.[4] Damage in the right carotid artery system causes difficulty with visual-spatial skills and with giving and understanding emotional messages. If the left anterior circulation is affected, a person often loses spoken and written language skills, the characteristic symptoms of aphasia.

2.2.2 Hemorrhagic stroke

In contrast to the insufficient supply of oxgen causing ischemic strokes, a hemorrhagic stroke arises from a bleeding into or around the brain. Depending on the source of the bleeding we can differentiate between intracerebral and intraventricular hemorrhages:

- *Intracerebral hemorrhages* can happen when tiny blood vessels at weak spots in the walls of small arteries inside the brain start to leak. Because the actual source of the bleeding is often small, it can take time for the loose blood to build up. That is why the symptoms of an intracerebral hemorrhage often increase over minutes or hours.
- *Intraventricular hemorrhage* occurs when the source of the bleeding is located close to or within the wall surrounding one of the brain ventricles. In these cases, the blood drains into the fluid-filled ventricular system, often sparing healthy brain tissue. A subarachnoid

[4] The symptoms can fluctuate in severity for hours and even days. If they appear temporarily, lasting a few minutes or hours only, they are called *transient ischemic attacks (TIAs).*

hemorrhage starts with a congenital weak spot on the wall of a major brain artery. This defect grows into a thin-walled pouch bulging out of the artery's side, shaped something like a berry. Such a condition is called an *aneurysm*. When the walls of the pouch grow too weak to hold the blood inside, it ruptures. The leaking blood may drain not only into the small space surrounding the brain but occasionally directly into brain tissue.

As the brain itself is not sensitive to pain, headaches from hemorrhagic strokes are believed to be due to either the stretching of the arterial wall when an aneurysm ruptures, the sudden increase of pressure within the skull, or the stretching of the membranes surrounding the brain.

In an (intracerebral) hemorrhage, the rapidly developing mass of blood in the brain usually causes symptoms resembling those of ischemic strokes. These include sudden weakness or numbness in one part or side of the body, abrupt confusion, visual problems, anosognosia, and frequently difficulties speaking or understanding language, i.e., aphasia, as well. Which brain functions are impaired and how badly depend mainly on the size and location of the bleeding. Unlike ischemic strokes, however, an (intracerebral) hemorrhage is more likely to cause a steady worsening of the initial symptoms, as blood continues to accumulate. Concurrently it is worth mentioning that hemorrhagic infarctions – even though they are often considered more serious than ischemic infarctions, because they seem more often to lead to death in the early stages – may yield better long-term results in aphasia if the patient survives. This is because hemorrhage tends to dissect its way between the brain cells and between white matter pathways, leaving many neurons temporarily but not permanently disabled, whereas occlusive ischemia destroys all cells deprived of oxygen (Helm-Estabrooks and Albert, 2004).

While both types of stroke, ischemia and hemorrhage, can cause language impairments or aphasia, the research project my thesis is based on, only included patients with ischemic strokes in the left hemisphere. This not without reason as a cerebrovascular accident in the *middle cerebral artery (MCA)* of the left hemisphere is the most frequent cause for damage to the language sensitive areas in frontal and temporal regions of the brain. Depending on the involvement of different blood vessels, different aphasia syndromes can be observed.

2.3 Aphasia assessment and classification

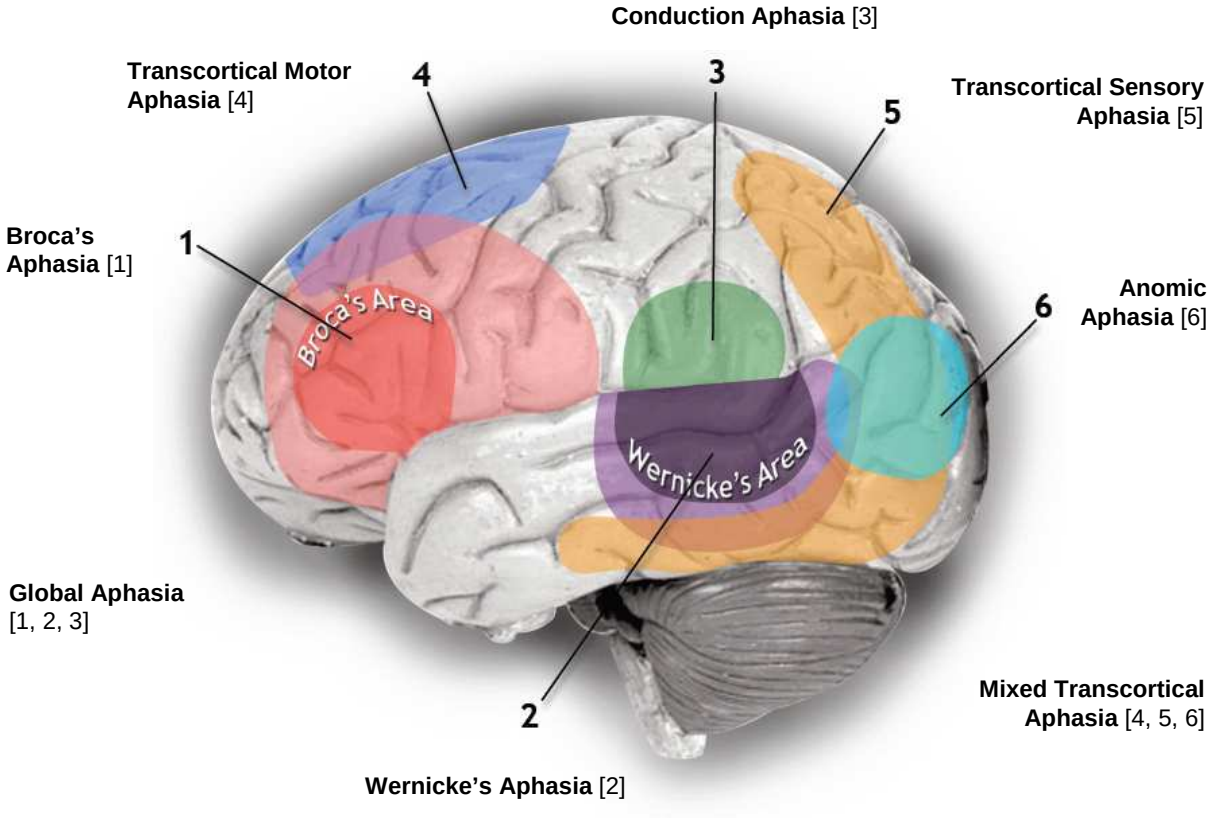
Aphasia can be assessed in a variety of ways which range from quick clinical screening at the bedside to several-hour-long batteries of tasks that examine the key components of language and communication. Aphasia test batteries measure aphasic symptoms in different language modalities through structured tasks in order to determine type and extent of the language disorder and to assign them to a clinical syndrome. The widely accepted and used psychometric

established aphasia batteries, e.g., the *Boston Diagnostic Aphasia Examination (BDAE)* or the *Aachen Aphasia Test (AAT),* usually include tests for fluency, comprehension, repetition, naming, reading and writing. It is a clinical tradition to classify aphasias on the base of typical combinations of linguistic errors which are revealed through these test batteries (see figure/table of classification below).

However, due to the difficulty of distinguishing between permanent structural brain damage and transient functional impairment in the acute stage of stroke, a reliable classification is only possible in a stable condition after stroke. Thereafter, several aphasia syndromes or types can be classified (Weniger, 2006):

- On the basis of vascular etiology four standard syndromes can be differentiated: *global, Wernicke (sensory), Broca (motor),* and *anomic aphasia.*
- In Addition, due to modality specific disturbance feature two further aphasia types can be distinguished: *conduction aphasia* and *sensory/motoric transcortical aphasia.*

Each of these characteristic aphasia types is usually associated with a specific brain region (see Figure/Table 2.2 below).



Figure/Table 2.2: Idealized distribution of lesions associated with different types of aphasia (figure own design, table below modified from Ross, 2010). Note that these relationships only hold for acute lesions and for a relatively short time period after injury because of the phenomena of long-term recovery of function.

	Syndrome	Spontaneous Speech	Fluency	Comprehension	Repetition	Naming	Reading	Writing	Associated Brain Region(s)
Nonfluent Aphasias	Global	Primarily speech automatisms (recurring utterances)	*Impaired*	*Impaired*	*Impaired*	*Impaired*	*Hardly possible*	*Hardly possible*	Occlusion of the internal carotid or middle cerebral artery, resulting in a large, wedge-shaped infarction of the frontal, temporal, and parietal lobes and deep portions of the middle cerebral artery territory.
	Broca	Difficulty with word finding; reduced sentence construction; agrammaticism	*Impaired*	*Spared*	*Impaired*	*Impaired*	*Impaired*	*Impaired*	The third frontal convolution of the left frontal lobe (BA44/45). Damage often extends down into the white matter and, in some cases, extends to nearby frontal regions, parietal operculum and the insula.
	Transcortical Motor	Problems with initiation of speech; similar to Broca's aphasia	*Impaired*	*Spared*	*Spared*	*Impaired*	*Spared*	*Impaired*	Supplementary motor area and frontal cortex anterior to Broca's area, but spares Broca's area.
Fluent Aphasias	Wernicke	Word finding difficulty: phonemic and/or semantic paraphasias; paragrammaticism; jargon	*Spared*	*Impaired*	*Impaired*	*Impaired*	*Impaired*	*Impaired*	Affects the inferior division of the middle cerebral artery that supplies the temporal cortex while sparing the frontal motor cortex; usually involves the posterior third of the superior temporal gyrus; Involvement of deep temporal white matter, the middle or inferior temporal gyri, or the inferior parietal lobule.
	Conduction	Word finding difficulty; phonematic paraphasias	*Spared*	*Spared*	*Impaired*	*Impaired*	*Impaired*	*Impaired*	Lesions in the arcuate fasciculus connecting the temporal and frontal language cortices; The supramarginal gyrus is often affected in conduction aphasia.
	Anomic	Naming difficulties: compensatory strategies and semantic paraphasias	*Spared*	*Spared*	*Impaired*	*Impaired*	*Hardly possible*	*Hardly possible*	Less specific in lesion localization than the other syndromes. Anomia may occur with lesions in the dorsolateral frontal cortex, temporal or temporo-occipital cortex, or thalamus.
	Transcortical Sensory	Word finding difficulties: semantic paraphasias	*Spared*	*Impaired*	*Spared*	*Impaired*	*Mostly Impaired*	*Impaired*	Bilateral lesions in the parieto-occipital cortex or a lesion in the left temporo-occipital cortex.

Unlike the conventional classification approach based on test batteries our research group attempted to develop a type of classification by looking at different aspects of aphasia and by utilizing the possibilities of new technologies. Since most patients have lesions which not only include grey but extend to the underlying white matter, we used a novel approach relating lesion size to white matter language fiber tracts and impairment of speech production (Marchina et al., 2011). This new method introducing the variable *lesionload* complements established voxel-based lesion mapping techniques and allows us to differentiate 3 language tracts (see Figure 2.3): the arcuate fasciculus (AF), the uncinate fasciculus (UF), and the extreme capsule (EmC) fiber system. Their predictive ability was assessed by relating them to various aphasic symptoms.

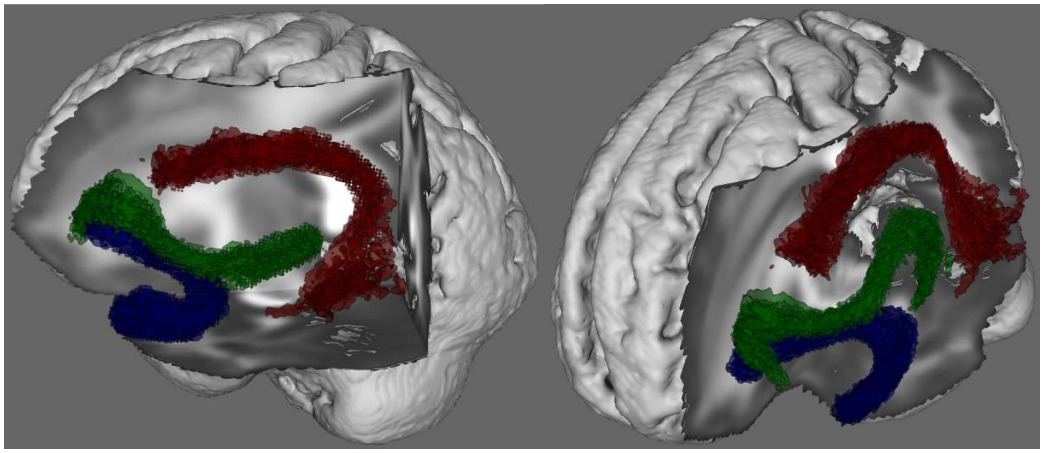


Figure 2.3: Visualization of the 3 white matter fiber tracts assumed to be involved with language processing. In red: the arcuate fasciculus (AF), green: extreme capsule fiber system (EmC), blue: uncinate fasciculus (UF).

2.4 Prognosis and recovery from aphasia

The prognosis of those with aphasia varies widely. According to Naeser and Palumbo (1994) the recovery process mainly depends on the localization and the extent of the ischemic lesion in the dominant hemisphere, but the age of the patient or the type of aphasia can have an effect as well. The identification of specific factors most important in determining the extent of recovery from aphasia has been subject of many investigations (for review see Lazar and Antoniello, 2008). Among the discussed factors involved in recovery from aphasia, the location and the size of the lesion seem to be particularly in the focus and the widely discussed factors important for recovery (Kertesz et al., 1979; Pedersen et al., 1995).

- From studies which have investigated how far *lesion location* can predict the aphasia severity for potential for recovery (Kertesz et al., 1993; Naeser et al., 1989; Selnes et al., 1983), it appears that there are critical areas within the language responsible networks that when injured or spared from damage have an important influence on fluency and comprehension recovery. However, due to the enormous variability in recovery across individuals with lesions in the same location, the clinical significance is debatable.
- Studies which examined the influence of *lesion size* on recovery disagreed largely in their conclusions. While Kertesz et al. (1979) found recovery to be proportional to lesion size, Pedersen et al. (1995) also found lesion size to be a significant independent influence on recovery whereas Laska's group found no significant difference in lesion volume between those who recovered completely and those who did not (Laska et al., 2001).

Over all, the large variability of symptoms and the dissimilar outcomes makes it still difficult to predict language recovery after stroke. All the more our novel and aforementioned approach relating lesion size to white matter language fiber tracts and impairment of speech production (Marchina et al., 2011) should be noted here because it promises to have the potential to estimate recovery potential after stroke and refine inclusion criteria for experimental rehabilitation programs.

2.5 Treatment/therapy of aphasia

So far there are no universally accepted methods for the treatment of aphasia, which makes the field of potential interventions large and somewhat complex. However, there is strong evidence that receiving treatment already in an early stage after the stroke is superior to just spontaneous recovery alone (Holland et al., 1996; Robey, 1994). Most interventions in the subacute phase are conducted by speech therapists who evaluate patients' individual needs, then use a combination of techniques to help recover language. Studies looking at treatment

effects in general include a wide variety of approaches such as biological (Small and Llano, 2009) and pharmacological (Liepert, 2008) approaches, various speech therapies, e.g., constraint induced therapy (Cherney et al., 2008; Pulvermuller et al., 2001; Szaflarski et al., 2008), or transcranial direct current stimulation (tDCS) (Monti et al., 2008) and transcranial magnetic stimulation (TMS) (Naeser et al., 2005a) to modulate the language network.

In his review from 1998, Albert points out that the critical clinical issue in current approaches to aphasia therapy is the necessity to individualize the therapeutic modality for the specific aphasic sign or symptom being targeted and the specific person being treated (Albert, 1998). He describes a variety of approaches such as a psycholinguistic approach, cognitive rehabilitation which not only focuses on linguistic competence but also on related neurobehavioral functions such as attention or memory, output-focused therapy (e.g., Melodic Intonation Therapy), an attempt to improve communication via computer (computerized visual communication) and even stresses the importance treating the person as a whole respect psychosocial aspects.

The most effective means of treating aphasia after stroke has yet to be determined, and studies investigating the efficacy of speech and language therapy for patients have yielded conflicting results. Bhogal and colleagues offer as an explanation for the observed heterogeneity of findings the difference in intensity of therapy (Bhogal et al., 2003). Another reason could be that, because the neural processes that underlie post-stroke language recovery remain largely unknown, it has not been possible to effectively target those using specific therapies. But with the advent and availability of modern brain imaging methods the plasticity of the human brain definitely advanced to a main topic within the field of cognitive neuroscience and beyond. Thus, there is good reason for gaining new perspectives by investigating an auspicious therapy approach such as Melodic Intonation Therapy (MIT) further, aiming to fill an important research void.

3 Melodic Intonation Therapy (MIT)

For more than 3 decades Melodic Intonation Therapy (MIT) has been considered as one of the most promising therapies for the treatment of aphasia. There are two important factors which fuel the enthusiasm and the positive expectations related to MIT: one is the complex phenomenon of brain plasticity and the other the rather puzzling observation that some patients with severe aphasia can produce correct words when singing, but not when they are asked to speak them (Gerstman, 1964; Geschwind, 1971; Hebert et al., 2003). While the topic of plasticity is

discussed in chapter 4, the present chapter gives a brief overview of the history of MIT and shows how the mentioned surprising observation led to the development of MIT.

3.1 Brief history of MIT

The observation that some individuals with severe aphasia can produce correct words only when singing (e.g., Goldstein, 1942) prompted clinicians to recommend the use of music and rhythm in the treatment of aphasia. 1904 Charles Mills suggested to play the piano, and encourage patients to sing popular songs (Mills, 1904). Despite of the psychological benefit, it may have little effect on propositional or conversational speech skills. Experience indicates that it is difficult to dissociate words stronlgy associated with a particular tune. For patients it is unlikely to be able to extract a word from a familiar song and using that word for purposeful communication. In 1945 speech pathologist Ollie Backus suggested to present useful words and phrases to patients with aphasia in a rhythmical, unison fashion (Backus, 1945).
It was only at the beginning of the 1970s when Albert, Sparks and Helm began to explore the use of a singing technique to facilitate and stimulate the propositional speech of severely nonfluent patients. In addition to clinical experience with patients who produced words only when singing, we were encouraged by emerging research evidence that the right cerebral hemisphere was important in mediating musical stimuli and intonational contours (Blumenstein and Cooper, 1974; Bogen and Gordon, 1971). Hypothesizing that functions associated with the intact right hemisphere might be tapped to improve the language functions of a damaged left hemisphere, Albert and his colleagues developed the technique known as Melodic Intonation Therapy, or MIT (Albert et al., 1973; Helm-Estabrooks, 1983; Sparks et al., 1974; Sparks and Deck, 1986; Sparks and Holland, 1976).

3.2 General description of MIT

MIT is a hierarchically structured program divided into three levels (for a detailed description see Helm-Estabrooks and Albert, 2004; Helm-Estabrooks et al., 1989):

- In the first two levels, multisyllabic words and short, high-probability phrases are musically intoned.
- The third level introduces longer or more phonologically complex sentences. These longer sentences first are intoned, then produced with exaggerated speech prosody, and, finally, spoken normally.

On all intoned phrases, the clinician taps the patient's left hand once for each syllable. Items

are intoned very slowly, with continuous voicing, using simple high-note/low-note patterns based on the normal speech prosody of the phrase.

As opposed to singing, melodic intonation uses a limited range of musical notes. The musical pattern is similar to that of the recitative which occurs in operas. Important to mention is as well that melodic intonation should have a slower and more lyrical tempo than speech, with more precise rhythm and more accentuated points of stress (Norton et al., 2009; Sparks and Holland, 1976). Pictures to illustrate target items are used to help stimulate patient response (Helm-Estabrooks and Albert, 2004; Helm-Estabrooks et al., 1989; Norton et al., 2009; Sparks and Holland, 1976).

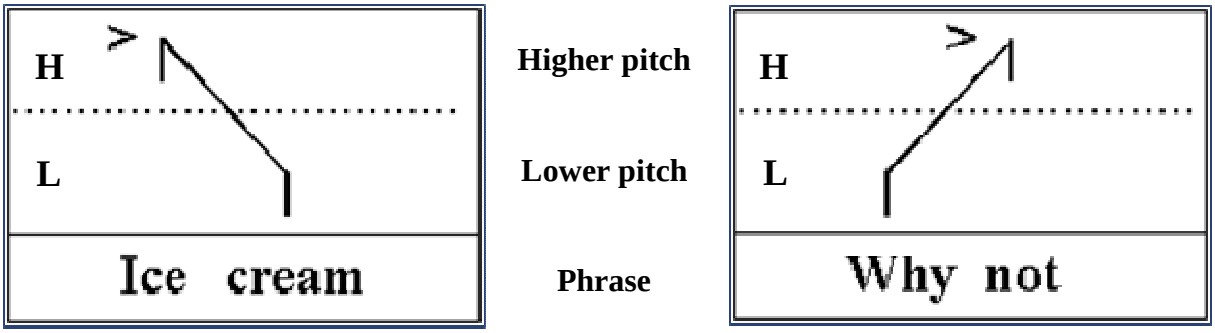


Figure 3.1: Spoken phrases (prosodic patterns) transposed into melodic intonation patterns (modified from Sparks et al. (1974)). Pitches are determined by the natural prosody of speech-accented syllables are presented on the higher of the two pitches.

3.3 Early cases and later studies

The first description of the effects of MIT on 3 patients with severe but not global aphasia in 1973 (Albert et al., 1973) was followed by a 1974 study of 8 patients of which 6 had notable improvement in propositional speech with MIT (Sparks et al., 1974). The authors concluded in a discussion about the mechanisms for improvement that it is unlikely that the undamaged right hemisphere is suddenly starting to speak for itself, but instead suggested that the right hemispheric dominance for melodic aspect of speech facilitated recovery of residual left hemisphere speech skills. A study by Carlomango and colleagues in 1997 seemed to confirm this as they did not find increased right hemisphere activation, but rather activation of undamaged left hemisphere areas (Carlomango et al., 1997). In 1994, the American academy of Neurology subcommittee for assessing therapeutic and technological methods recruited a panel of expert to review the safety and effectiveness of MIT (Neurology, 1994). This is the first and to date only speech therapy method so reviewed.

Since the invention of MIT only a few studies have systematically examined the effects and

efficacy of the method. Most of them had a very small number of subjects and the methods which were used vary greatly. The group around Laine examined three aphasic patients of whom two had non-fluent and one fluent aphasia using *single photon emission computer tomography (SPECT)* (Laine et al., 1994). The non-fluent patients did not respond to MIT and none of the three patients showed higher activation in the right hemisphere. The authors concluded that either the right hemisphere activation hypothesis is incorrect or it holds true only for good responders to MIT. A *positron emission computer tomography (PET)* study likewise showed no activation in the right hemisphere during repetition with MIT, but abnormally activated the same without using MIT (Belin et al., 1996). Since the recovery process induced by MIT coincides with reactivation of left prefrontal structures, the study supports the idea that abnormal activation pattern in the lesioned brain are not necessarily related to the recovery process. A plain behavioral study investigated the effect of a Persian version of MIT on 7 non-fluent aphasia patients (Bonakdarpour et al., 2003). Improvement in the selected variables were shown to be significant after treatment, but not during the treatment-free phase. And the authors did not find any generalization to non-targeted variables. A very recent study by our group (Schlaug et al., 2008) compared MIT with a control intervention in two patients. While both interventions revealed significant improvement in propositional speech that generalized to unpracticed words and phrases, the MIT treated patient's gains surpassed those of the control-treated patient. Imaging changes associated with treatment show an engagement of the right hemisphere, which accounts for its effect over non-intoned speech therapy. Likewise two patients were examined in a study conducted by Breier and colleagues in 2009. Using *Magnetoencephalography (MEG)* both patients exhibited increased left hemisphere activation after MIT. However, the good responder to therapy showed decreased activation in right hemispheric language-homolog areas, while the poor responder showed increased activation in these regions (Breier et al., 2009b).

For this thesis project modern neuroimaging methods such as fMRI and DTI as well as a newly developed technique called *lesionload* were used to examine the therapy outcome on a functional level, but furthermore in order to predict the recovery potential of Broca's aphasics using MIT and thereby get information about the efficacy of this particular treatment method. Some of the obtained results were discussed in the framework of the language model proposed by Hickok and Poeppel (2004).

4 Aphasia and plasticity

"The principal activities of brains are making changes in themselves."

Marvin L. Minsky

By using both, melodic and rhythmic aspects and an intense treatment process, MIT tries to facilitate the use of language by the non-dominant right hemisphere. It may exert its effect by either unmasking existing music/language connections in both hemispheres or by engaging preserved language capable regions in either or both hemispheres. MIT obviously utilizes the potential to change and reorganize the brain through intense treatment and is therefore a very illustrative example for plasticity in the brain.

4.1 Brain plasticity in general

The brain's ability to change its organization as a result of experience is referred to as neuroplasticity or brain plasticity. The polish neuroscientist Jerzy Konorski first introduced this concept to the scientific literature (Konorski, 1948). Although research highlighted the importance of neuroplastic processes, it took some time until this concept was widely accepted. The invention of modern brain imaging techniques boosted the plasticity research and studies in healthy subjects showed that the brain can not only be changed through intense practice, but by that these changes can as well disappear when practicing stops (Jancke, 2009b). This knowledge inspired Jancke (2009b) to introduce the metaphor "use it or lose it" as a way of expressing the fact that plasticity is possible in all directions.

Plastic changes of the nervous system can occur in the normal development and maturation of the organism (developmental plasticity), but have also been observed in the adult brain as a result of injury (lesion-induced plasticity) or acquisition of new skills (learning-induced plasticity) (Irvine et al., 2006). The mechanisms of neuronal plasticity which have been investigated for many years were first suggested by two scientists who presented the hypothesis that the coupling between neurons (i.e., the synapse) is responsible for learning by changing its efficacy (Cajal, 1911; Hebb, 1949). The ideas of Hebb are often paraphrased as 'neurons that fire together wire together' and are commonly referred to as *Hebb's Law*. More than 20 years later, scientists for the first time were able to support the Hebbian theory when they observed an increase in synaptic efficacy that lasted for a long time (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973). Long-term potentiation of synaptic efficacy can last for days or months and is assumed to be the neuronal basis for the initial steps in the process of brain plasticity.

4.2 Reorganization and recovery after stroke

The natural recovery process after extensive damage to the language areas can be divided into three overlapping stages (acute, subacute, chronic), each with different underlying neural mechanisms (Hillis, 2005; Hillis and Breese, 2003):

- *Acute* recovery which is due to restoration of tissue function occurs in the hours to days following brain damage. After the existence of the ischemic penumbra[5] was reported (Olsen et al., 1983), several recent studies support the proposal that immediate recovery of language after stroke is more likely due to reperfusion of the ischemic penumbra than due to reorganization (Hillis et al., 2002; Hillis et al., 2003). However, there is some evidence that early reorganization of the motor or sensory functions may also occur through expression of neural plasticity and contribute to recovery of language tasks that require these functions. (e.g., Jenkins and Merzenich, 1987). While these results indicate a role of reorganization in the acute phase of recovery, it was assumed that language relies on a more complex network of connections that probably takes more time to reorganize than do basic sensory or motor functions (Marsh and Hillis, 2006).
- The *subacute* stage of recovery follows the acute phase and lasts for several weeks to months during which new connections are formed and synaptic efficacy changes. Again, there are two possible components one of which is *diaschisis*[6] (von Monakow, 1914). The theory is that the dysfunction is due to hypometabolism that occurs downstream in a neural network as a result of the loss of neural input from the damaged area. Additional input from other, undamaged areas of the brain restoring the function can lead to recovery. The other component is again neural plasticity that causes reorganization of both structure and function.
- *Chronic* recovery consists of compensation of reorganization of cognitive function. This phase begins months to years after injuries such as stroke and may continue for the rest of the person's life. During this phase recovery of language is achieved by learning new ways to retrieve language representations and establishing compensatory strategies.

[5] An area of the brain surrounding the ischemic infarct that remains viable for some time, but is dysfunctional because it is receiving low blood flow.

[6] *Diaschisic* describes the loss of function in a portion of the brain that receives input, but is distant from the site of injury.

4.3 Recovery and location of reorganization – evidence from neuroimaging studies

A large body of evidence shows that reorganization occurs, allowing at least partial recovery of language following injury, however, the areas that are responsible for assuming the lost function remain controversial. Many functional imaging studies have shown activation in the homologous areas of the *right hemisphere* during language tasks in patients with lesions in the left hemisphere who have recovered from aphasia (Basso et al., 1989; Cappa et al., 1997; Kinsbourne, 1971; Weiller et al., 1995). Other studies in turn suggest that regions surrounding lesions in the *left hemisphere* assume function after damage to language areas (Heiss et al., 1997; Karbe et al., 1995; Karbe et al., 1998; Thiel et al., 2001; Warburton et al., 1999). And even *bilateral* activation patterns were reported by a few research teams (Heiss and Thiel, 2006; Mimura et al., 1998; Rosen et al., 2000; Saur et al., 2006; Winhuisen et al., 2005).
This is not just an apparent contradiction, but in addition there is an ongoing controversy on whether the activation observed on the right hemisphere is abnormal and maladaptive or well-adapted functional reorganization (Belin et al., 1996; Raboyeau et al., 2008). Marsh and Hillis (2006) try to reconcile this contradiction giving 3 possible explanations:

- It has been proposed that both the right and the spared left hemisphere areas contribute to recovery, but the location and extent of recovery depend on the extent of the damage, the duration of the injury and which language function are affected.
- Another possibility is that both hemispheres are always very much involved in the recovery process as shown by studies in different modalities (Menke et al., 2009; Noppeney et al., 2005; Saur et al., 2006).
- The third explanation suggests that language initially switches to the contralateral hemisphere following damage until the left hemisphere can be reintegrated into the language network. Several studies propose that those patients who are able to shift language function back to the left have the best chance of good recovery (Heiss et al., 1999a; Marshall et al., 2003; Rosen et al., 2000; Small et al., 1998).

The neural correlates of treatment is examined by an increasing number of studies by contrasting *post versus pre therapy assessment* (e.g., Cherney and Small, 2006; Meinzer et al., 2007; Vitali et al., 2007). The large variety of designs, treatment types, treatment intensities and imaging tasks makes it difficult to compare and draw a conclusion. In addition, due to the use of rather small subjects' samples the explanatory power of these studies is relatively small. One possible explanation for the observed heterogeneity of findings across studies is a

difference in *intensity of therapy* (Brindley et al., 1989; Poeck et al., 1989). It was concluded that intense therapy over a short amount of time can improve outcomes of speech and language therapy for stroke patients with aphasia (Bhogal et al., 2003).

5 Methods

In this chapter on methods the two main neuroimaging techniques utilized in the conducted studies (chapter 6) will be described:

1.) *functional magnetic resonance imaging (fMRI)* which is a type of specialized MRI[7] acquisition measuring the change in blood flow related to neural activity in the brain or spinal cord of humans and which has come to dominate the brain mapping field since the early 1990s due to its low invasiveness, absence of radiation exposure, and wide availability (chapter 5.1);

2.) *diffusion tensor imaging (DTI),* a relatively new application of magnetic resonance imaging which uses diffusion properties of water through axons and can quantify the directional dependence of water diffusion in biological tissue (chapter 5.2).

Note that this chapter does not go far beyond a condensed description of the basic principles of both of these methods.[8] The consideration of crucial methodological issues and challenges we concretely encountered during the course of our studies will be discussed in the concluding part of this dissertation (chapter 7.1).

5.1 Functional magnetic resonance imaging (fMRI)[9]

Functional magnetic resonance imaging (fMRI) has revolutionized cognitive neuroscience over the past decade. It has provided a unique opportunity to gain insight into the organization of human brain by relating behavioral measures to underlying brain activation. It has rapidly become an important tool in clinical medicine and biological research and is currently the most widely used method for brain mapping and studying the neuronal basis of human cognition. The following chapters have the goal to introduce the basics of fMRI with a view to as-

[7] Magnetic resonance imaging (MRI) is a noninvasive medical imaging technique used in radiology to visualize detailed internal structure and limited function of the body. It provides much greater contrast between the different soft tissues of the body than *computed tomography (CT)* does, making it especially useful for brain imaging.

[8] For further details see one of the numerous excellent and popular textbooks, e.g. Jaencke (2005) and Mori (2007).

[9] For an excellent overview cf. Jaencke (2005).

sure a better understanding for the underlying physics, the procedure in general and the different possible paradigms to avoid the problems of the interfering scanner noise.

5.1.1 Basic principles of MRI scanning

Magnetic components and larmor frequency

Magnetic resonance imaging (MRI) measures the response of hydrogen molecules to a perturbation while in a magnetic field. MRI is based on the principles of *nuclear magnetic resonance (NMR),* a property of atoms first observed by Bloch (1946) and Purcell et al. (1946). The technique was called magnetic resonance imaging rather than *nuclear magnetic resonance imaging (NMRI)* because of the negative connotations associated with the word nuclear in the late 1970s.

The reason for using the hydrogen nucleus is that it exists abundantly in the human brain and gives a relatively strong MRI signal (Buxton, 2002; Horowitz, 1995). Hydrogen nuclei are positively charged particles that spin around their axis. When an electrically charged particle moves, it produces a magnetic field, which can be represented by a vector or *Magnetic Dipole Moment (MDM)* with both magnitude and direction (Buxton, 2002; Horowitz, 1995). Placing the brain in a magnetic field aligns the hydrogen nuclei – which previously pointed into random directions – in the direction of the main magnetic field (like a compass aligns with the field of the earth). The nuclei will tend to assume one of two states: 1) parallel (low energy), 2) antiparallel (high energy). A slightly greater numbers of protons exist in the parallel direction.[10]

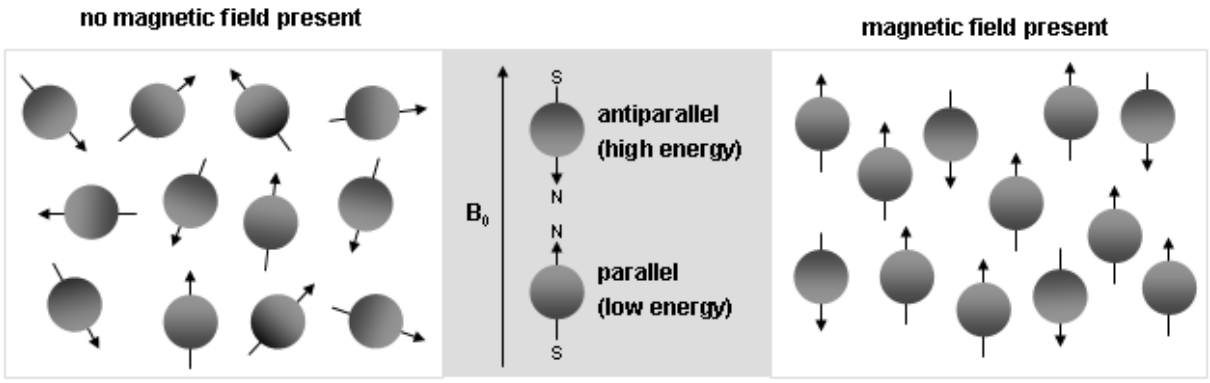


Figure 5.1: Spinning protons and their alignment in a magnetic field (own design following Jaencke (2005) and Gaab (2004)). A net magnetization is produced following the application of an external magnetic field causing a small majority of spins to align in the direction of the applied field (parallel direction).

[10] The high resolution in MRI is thus not explained by the high level of energy involved but rather by the amount of hydrogen protons in water and fat (6 million protons in one voxel of water).

How many nuclei align themselves to this field is dependent on the strength of the magnetic field – the stronger the field, the more nuclei align themselves to it (Buxton, 2002; Horowitz, 1995). Furthermore, within the magnetic field the MDM's of the nuclei start to precess with a frequency that is dependent on the type of the nucleus and is directly proportional to the strength of the magnetic field (the stronger the field the higher the precession frequency). This relationship is expressed by the *Larmor equation:*

$$\omega_0 = \gamma B_0$$

ω_0	resonance frequency (or larmor precessional)
γ	gyromagnetic ratio (a constant unique to every atom)
B_0	main magnetic field, measured in Tesla

Signal detection

When an electromagnetic *radio frequency (RF)* pulse is applied at the larmor frequency the protons are able to absorb that energy. This means that more protons flip from 'aligned with' to 'aligned against' B_0, thus gaining a higher energy state and hence changing the net magnetization. The magnetization vector, Mø, spirals down towards the XY plane or the negative Z axis. This tipping-down angle α is a function of the strength and duration of the applied RF pulse. A short and weak RF pulse can cause a 10 degrees flip angle and a longer and/or stronger pulse can produce a 90 degrees angle.[11] Over time this energy which was poured into the system by the RF-pulse, is released when the MDM's return to their original state. This release of energy is known as *relaxation* and this is the radiofrequency signal that is measured during MRI (Buxton, 2002; Horowitz, 1995).

Relaxation (see Figure 5.2 below)

T1 is the time constant characterizing the rate at which excited nuclei dissipate excess energy to the environment (lattice). We refer to this as the *spin-lattice or longitudinal relaxation time*. T1 is the time it requires for longitudinal magnetization to relax back to 63% of its initial value. It represents an exponential time constant and not the time for full recovery.[12] Since the number of spin-lattice interactions is dependent on the precessional frequency of protons, the T1 relaxation time depends on the magnetic field strength which means that T1 values

[11] Cf. http://rad.usuhs.mil/rad/handouts/fletcher/fletcher/index.htm

[12] After 5 T1 the sample is considered to be back to full longitudinal magnetization. T1 values range from 0.1 to 1 second in soft tissues and from 1 to 4 seconds in aqueous tissues and water.

increase with magnetic field strength.

T2 is the time constant characterizing the rate at which excited nuclei exchange energy, or go out of phase, with each other. We refer to this as the *spin-spin or transverse relaxation time*, because it is the loss of transverse magnetization that determines the T2 relaxation time. The elapsed time between the maximal transverse signal and 37% of the maximum is the T2 decay constant. Unlike T1 values, T2 values are not related to field strength. Pure T2 decay is a function of completely random interactions between spins.

As relaxation time rules of thumb we can presume that T2 and T1 mechanisms are related to the rotational and tumbling frequency of molecules. Small molecules reorient more rapidly than larger molecules. The quicker a molecule reorients, the less dephasing is caused by adjacent protons. Small molecules (e.g., liquids) exhibit shorter T1 and longer T2. Large molecules (e.g., lipids) tend to have longer T1 and shorter T2 value.[13] Figure 5.2 visualizes various relaxation times for different brain tissues such as *fat (F), white (WM)* and *grey matter (GM)*, on the one hand, and *cerebrospinal fluid (CSF)*, on the other hand.

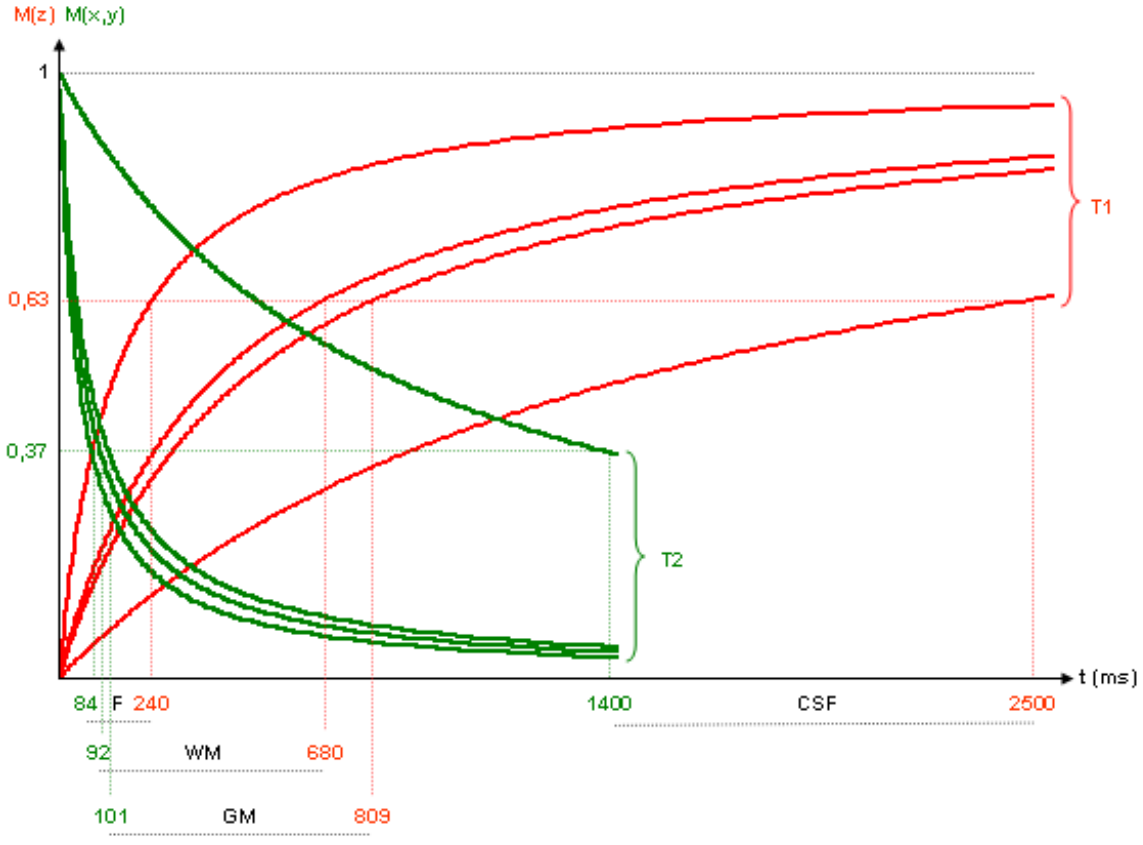


Figure 5.2: Tissue dependent relaxation time constant for T1 and T2 (own design following Jaencke (2005)). After radio frequency excitation the spins will tend to return to their equilibrium distribution in which there is no transverse magnetization and the longitudinal magnetization is at its maximum value and oriented in the direc-

[13] Cf. http://rad.usuhs.mil/rad/handouts/fletcher/fletcher/index.htm

tion of the static magnetic field. The transverse magnetization decays toward zero with a characteristic time constant T2, and the longitudinal magnetization returns toward equilibrium with a characteristic time constant T1.

If the time from RF-pulse to measurement of the signal called *Echo Time (TE)* is kept short, while simultaneously the time between two successive RF-pulses called *Repetition Time (TR)* is also kept short, the difference in T1 for the different tissues is maximized and the acquired scan is called a *T1 weighted scan*. Alternatively, if the TE is long while at the same time the TR is also long, the difference in T2 for the differnt tissues is maximized and the acquired scan is called a *T2 weighted scan*. These are sometimes referred to as pathological scans, because lesions appear very bright (Horowitz, 1995; Jezzard and Clare, 2001).

The BOLD contrast in fMRI

Functional MRI (fMRI) refers to the mapping of specific brain activity using the *blood oxygenation level dependent (BOLD)* contrast. In fMRI neuronal activity is not measured directly, but rather captures changes in the inhomogeneity of the magnetic field, which are a result of changes in the level of oxygen present in the blood (Heeger and Ress, 2002; Ogawa et al., 1990; Ogawa et al., 1992). Neuronal activity causes a rise in cerebral blood flow, which leads to a change of the local ratio between oxy- and deoxyhaemoglobin (*hemodynamic response function or HRF*) (Gazzaniga et al., 2002; Heeger and Ress, 2002). Deoxy- and oxyhaemoglobin have different magnetic properties: *deoxyhaemoglobin* is paramagnetic and introduces an inhomogeneity into the nearby magnetic field, whereas *oxyhaemoglobin* is weakly diamagnetic and has little effect. Hence, an increase in the concentration of deoxyhaemoglobin would cause a decrease in image intensity, and a decrease in deoxyhaemoglobin would cause an increase in image intensity (Heeger and Ress, 2002). The emerging model of the haemodynamic response in fMRI posits that there are three phases of the BOLD response to a transient increase in neuronal activity: an initial, small decrease in image intensity below baseline (during the initial period of oxygen consumption), followed by a large increase above baseline with a maximun after approximately 6 seconds (an oversupply of oxygenated blood, which is only partially compensated for by an increase in deoxygenated venous blood volume), and then by a decrease back to below baseline again after around 24 seconds (after the oversupply of oxygenated blood has diminished, it still takes some time for the blood volume to return to baseline) (Heeger and Ress, 2002). The BOLD signal in fMRI also depends on the inflow of fresh blood that has not experienced the same history of radio-frequency excitation. This inflow effect – by itself (in the absence of any of the aforementioned changes in deoxyhaemo-

globin concentration) – would appear as an increase in image intensity, and it adds to the increase in image intensity during the second phase of the response (Heeger and Ress, 2002).

5.1.2 Basic principles of fMRI data processing

Preprocessing in fMRI

The purpose of preprocessing in fMRI is to correct for non-task related variability in experimental data. These approaches are usually performed without any consideration for the experimental design and therefore are called preprocessing. The preprocessing steps seek to remove, rather than model data variability. One important term in fMRI analysis language is the *signal-to-noise ratio (SNR)*, which is the quotient between task-related variability and non-task-related variability. The goal of the preprocessing is to remove as much non-task-related variability as possible in order to obtain a high SNR value. The sensitivity of an fMRI analysis is determined by the amount of residual noise (non-task related variability) in the image series.[14] Thus, before the data analysis the recorded images are realigned, spatially normalised into a standard space, and smoothed.

Realignment (motion correction)

Small movements of approximately 1 mm occur (e.g., Franckowiak et al., 1997) even though the subject's head is fixated within a head coil and the subject tries explicitly not to move. Furthermore, there are movements related to physiological factors, such as cardiac and pulmonary parameters. These movements can e.g., alter the 'spin history' as a result to the change of position relative to the gradients of the scanner. By applying motion correction, artifacts due to small movements of the head can be removed or corrected. For this process, the functional volumes are aligned in space by rigid-body transformations applying a least square approach using 6 motion parameters in total: three translation parameters along the x, y and z-axes as well as three rotation parameters around those axes, i.e., pitch, jaw and roll (Friston et al., 1996). The first image in a time-series is used as a reference to which all subsequent scans are aligned. Motion correction has several limitations including artifact-related limitations which can result in a loss of data at edges of the imaging volume or ghosts in image do not change in the same manner as real data. Furthermore distortions in fMRI images may be dependent on position in the field, rather than on position in the head.

[14] Cf. http://www.biac.duke.edu/education/courses/fall03/fmri/handouts/W9_Preprocessing_Design_2003.htm and Gaab (2004).

Normalization

This preprocessing step spatially (stereotactically) normalizes images into a standardized space, which is defined by some ideal model or template image. It can thus be described as an intersubject averaging method. The SPM[15] software program conforms to the Montreal Neurological Institute (MNI) space and approximates that of the space described in Talairach and Tournoux's atlas (1988). Generally, these algorithms work by minimizing the sum of squares differences between the acquired images and the template. One major advantage of the normalization is that it allows the generalization of results to a larger population, thereby enabling averaging across subjects and improving comparisons with other studies. Normalization also provides coordinate space to report the results. One disadvantage of normalization can be cited in its potential to reduce the spatial resolution resulting from differences in interindividual brain organization and thus may reduce the activation strength by averaging subjects.

Spatial smoothing

The spatial smoothing involves the application of a filter to the image, which removes high-frequency information in order to improve the signal-to-noise ratio (SNR), compensate for residual between-subject variability after normalization, and approximate a random field for statistical purposes. The most common means of smoothing is by convolving the images with an isotropic Gaussian kernel. The amount of the smoothing is determined by the width of the distribution and is usually expressed in #mm *full width at half maximum (FWHM).* This measures the width of the distribution, at half of its maximum (Poldrack et al. 2011). In general it is recommended to use twice the voxel size of the images. Issues related to smoothing such as reduced spatial resolution are discussed in detail in Friston et al. (2000).

Statistical analysis of fMRI data

Many techniques have been proposed for statistically analysing fMRI data, and a variety of these are in general use. The aim of such analysis is to produce an image identifying the regions which show significant signal change in response to the task. Predominantly the *General Linear Model (GLM)* is used. The basic concept of the GLM is that it treats the data as a linear combination of model functions plus noise. Typically, these methods result in a statistical parametric map. The observed statistical map will then be represented at a given level (threshold) according to the point of distribution of the statistics (uncorrected level) or the

[15] SPM software is freely available to the (neuro)imaging community on http://www.fil.ion.ucl.ac.uk/spm/

field distribution of the statistics (corrected levels for local maxima). A correction to the significance of the t-statistics is suggested, which account for the multiple comparisons in the image. Overall, these methods are voxel-by-voxel hypothesis testing approaches, which reliably identify regions showing a significant effect of interest. The GLM model used can refer to a single subject, one group of subjects or multiple groups of subjects. Multi-subject fMRI experiments can also be performed using a GLM framework with different forms depending on the approach taken, e.g., fixed or random effects analysis. Fixed-effect models use data from all subjects to construct a statistical test which allows interference to the analyzed subject sample. A random-effects model however, accounts for inter-subject variance in analyses and permits interference to population from which subjects are drawn, which is essential for group comparisons.

5.1.3 Auditory stimulation and fMRI

Problems of auditory experiments

The application of functional neuroimaging to conduct auditory and overt speech research is more problematic than for other sensory modalities, because of the difficulty of delivering high-fidelity calibrated stimulation in the high magnetic fields, and the intense masking noise generated by the MR scanner (Hall et al, 1999). This intense stray masking noise resulting from mechanical forces created by the switching of the gradient coils every time the MR signal is read out. Scanner noise in *Echo Planar Imaging (EPI)* sequences can 1) interfere with the auditory stimulation (Bandettini et al., 1998; Hall et al., 2000), 2) lead to masking of the auditory cortical or speak response depending on the frequency of the MR acquisition (Shah et al., 1999), 3) lead to activation of the auditory cortex itself depending on the effective *repetition time (TR)* for MR acquisitions (Bandettini et al., 1998; Ulmer et al., 1998), and 4) lead to differences in the attentional demands if frequency and intensity of the MR scanner noise differ between studies

Several methods addressing the problem of the scanner noise have been discussed in the literature. This includes modifications of the hardware components of the scanner (e.g., Mansfield et al., 2001) as well as alterations of the software (e.g., Hennel et al., 1999) used for the experiments. A number of studies have also suggested modifications of the experimental design. For a review of the current strategies and future prospects of dealing with the acoustic noise in fMRI see Amaro et al. (2002). One such method is *sparse temporal sampling* which was used by us for the conducted fMRI studies.

The sparse temporal sampling method

Sparse imaging (see Figure 5.3) uses a clustered-volume acquisition sequence to reduce intravolume noise interference. By increasing the *interstimulus interval (ISI)* between each set of data acquisitions, i.e., increasing the *repetition time (TR),* the rate of the bursts of scanner noise is reduced and consequently the intervolume noise interference decreases. This ensures that the measured activity in the auditory cortex is uncontaminated by its responses to the preceding burst of scanner noise.

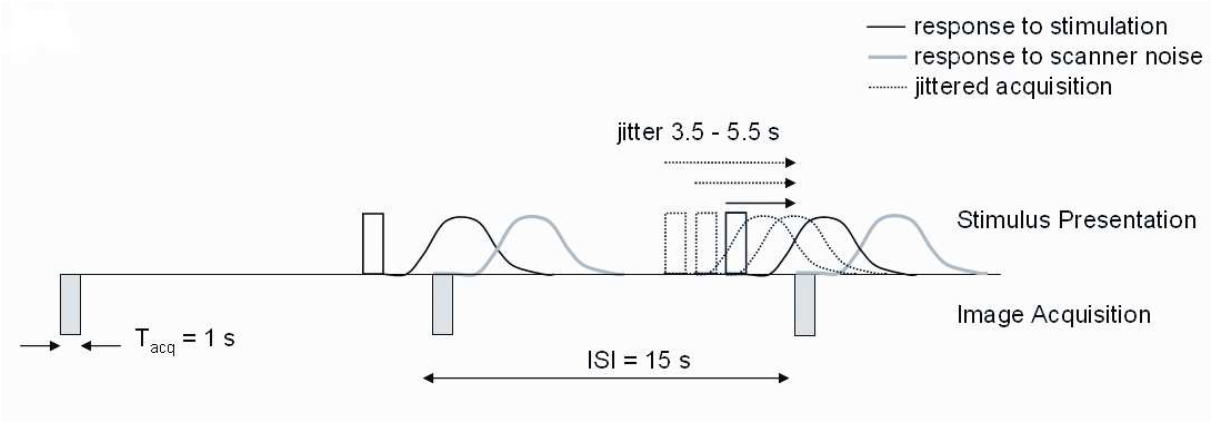


Figure 5.3: The sparse temporal sampling acquisition technique.

Sparse temporal sampling is characterized by the acquisition of only one volume during each epoch. Therefore it is needed to acquire images near to the maxima and minima of the mean haemodynamic response since imaging the auditory cortex at these two time points will enhance signal detection (Hall et al., 1999). Hall et al. (1999) compared continuous scanning with a sparse temporal sampling method, using an effective TR of 14 s, and revealed a greater MR signal change for acquisitions with a long TR. Hall et al. (1999) showed further that the activation reached its maximum at 4-5 s after stimulus onset and decayed after an additional 5-8 s. Other researchers have shown a decrease in the spatial spread and lower z scores of the activated auditory regions dependent upon the duration of the MR scanner noise (Shah et al., 1999). Belin et al. (1999) used an effective TR of 10 s and varied the delay between a short auditory stimulus and the MR acquisition. The maximum was measured in the primary auditory cortex 3 s after stimulus onset and had a duration of 3 s (Belin et al., 1999). Gaab et al. (2003) modified the sparse temporal sampling technique by acquiring one set of volumes every 17 s (TR = 17 s). Although the TR was kept constant at 17 s, the MR acquisition actually varied with regard to the auditory stimulation by altering the onset of the auditory stimulation within the 17 s time frame, which varied the delay between the end of the stimulation and the onset of the next MR acquisition. By refining the sparsed technique Gaab et al. (2003) were

able to discern the functional anatomy and the time course of cerebral activations.
In sum, Hall et al. (1999) suggest that the sparse imaging paradigm is advantageous in auditory experiments for three reasons. First, sparse imaging ensures that the activation is not a result of some interaction between the stimulus and scanner noise. Second, the MR signal-to-noise ratio (SNR) is enhanced, despite fewer data samples than used with continuous scanning and the consequent loss of statistical power. Last but not least sparsed imaging reduces the discomfort and even stress caused by the loud scanner noise during data acquisition.

5.2 Diffusion tensor imaging (DTI)[16]

Diffusion tensor imaging (DTI) is a relatively novel non-invasive imaging technique that provides insights into aspects of brain structure that could never be studied before in living humans. The technique therefore has a huge potential for addressing novel research questions in both basic and clinical neuroscience. Due to its non-invasive nature and ready availability diffusion data has opened up the field of neuroanatomy to an array of researchers who originally specialized in other areas of neuroscience. The sensitivity of diffusion measures to white matter change, offers a unique insight into the structural organization of the brain white matter.
The following chapters describes the most basic principles underlying diffusion imaging and tractography and discusses briefly two main classes of algorithms – deterministic and probabilistic tracking. The final chapter 5.2.4 gives a short summary of DTI studies conducted in the field of stroke recovery and aphasia.

5.2.1 Basic principles of DTI

Diffusion

Robert Brown discovered and described the phenomenon of self-diffusion of water molecules, i.e., the random translational motion of molecules as a result from the thermal energy carried by these molecules, after he realized that it was not the particles in the water which were moving of their own volition, but the water molecules that they were suspended in (Brown, 1828). This is today known as *Brownian motion* and represented by the diffusion term D. Single water molecules undergo independently from each other a completely random trajectory. It can be described as a 'random walk' whereby it is meant that a molecule stays in a particular

[16] An excellent overview is offered by Jones (2008). For a very detailed description cf. Johansen-Berg and Behrens (2009).

place for a fixed time, before moving into a random, new location in space. This process continues for each molecule which draws out a random path in 3-dimensional space. Even though we cannot say anything about one particular molecule, Einstein proved 1905 with his equation for Gaussian diffusion that in a sufficiently large number of particles which are free to diffuse, at least one aspect of the behavior could be characterized: the squared displacement of molecules from their starting point over a time, averaged over all the molecules in the sample is directly proportional to the observation time (Einstein, 1905). The distribution of squared displacements takes a Gaussian form – the peak being at zero displacement and the probability of displacing a given distance from the origin is the same and independent from the measured direction. In other words, diffusion MRI can measure the displacements of water molecules in a very small range (~ 5-10 µm) over a time span of tens of milliseconds.

Hindered diffusion

It is important to note that in diffusion MRI we do not measure a diffusion coefficient directly, but rather the mean displacement of water molecules within each voxel that forms the image. Cell membranes, macromolecules and so forth can be a hindrance for the water molecules along their random walk which results in a lower mean squared displacement per unit time, than when observed in free water. Thus, the diffusion coefficient appears to be lower than it is which led to the term *apparent diffusion coefficient (ADC).* This coefficient reflects the fact that we are subject to the effects of hindrances (Le Bihan et al., 1986). The average ADC in tissue is around four times smaller than in free water (Le Bihan et al., 1986). The observation that tissue microstructure affects apparent diffusion properties of water and that diffusion acts as a sensitive probe to any changes in cellular structure that alter the displacement per unit time, led to the introduction of *diffusion imaging* (Le Bihan and Breton, 1985).

Isotropic and anisotropic structures – influence on diffusion MR

The most useful clinical application of this new discovery to date is the use of *diffusion weighted (DW)* scans in acute ischemia. The lesion appears hyper-intense due to a reduction in the ACD and therefore less signal attenuation (Moseley et al., 1990b). However, at about the same time observations were made that the measured ADC was strongly dependent on the direction that it was measured (Moseley et al., 1990a). This is an effect of different diffusion properties of different media. Placing a drop of ink at the center of a cube of water makes the ink particles displace due to the thermal motion of its molecules (Jones, 2008). The outer profile of the displacements would resemble a sphere, since diffusion in isotropic media is iso-

tropic. That means that the displacements are equal in all directions as there are no oriented barriers to impede diffusion preferentially on one direction over another. The ink particles in an anisotropic medium would diffuse further along the principal axis and not in a perpendicular, suggesting a higher density of fibers oriented in this direction. In other words, *anisotropic diffusion* refers to the fact that the molecular displacements of water are not identical in all directions. In brain areas with *isotropic diffusion*, the diffusion-weighted intensity is the same, independent from the measured direction, suggesting that the ADC is the same in all directions. In anisotropic regions the measured diffusion weighted intensities vary greatly with the measured direction, indicating that in one or two axes something is hindering the displacement of water molecules and there is an underlying ordered structure that has a preferred orientation (e.g., right-left).

Since all these observations were initially made in the white matter of the mature adult brain, it was concluded that diffusion anisotropy is the result of myelin, acting as a hydrophobic barrier to diffusion (Thomsen et al., 1987). But anisotropy can be observed when myelin is absent (Beaulieu, 2002) and different other mechanisms were suggested including local susceptibility gradients (Hong and Dixon, 1992), axonal cytoskeleton and fast-axonal transport. Current view seems to state that the main determinant of anisotropy in various tissue is the presence of intact cell membranes and that myelination serves to modulate anisotropy (Beaulieu, 2002).

5.2.2 The diffusion tensor model

The diffusion tensor

In anisotropic or ordered tissue we can no longer characterize the behavior of water with a single ADC, since the ADC we measure depends on the direction in which we measure. And the more ordered the tissue the stronger that dependency gets. The *diffusion tensor* provides a model to describe Gaussian diffusion in which the displacements per unit time are not the same in all directions (Basser et al., 1994a). It is defined by a 3x3 symmetric matrix of numbers that characterize 3-dimensional displacements where the diagonal elements correspond to diffusivities along 3 orthogonal axes and the off-diagonal elements correspond to the correlation between displacements along those orthogonal axes. In practical terms this means that by applying a series of diffusion gradients (i.e., magnetic field variations in the MRI magnet) which can determine at least 3 directional vectors (use of 6 different gradients is the minimum and additional gradients improve the accuracy for ‘off-diagonal’ information), it is possible to calculate for each voxel a tensor that describes the 3-dimensional shape of diffusion.

The diffusion tensor ellipsoid

Taking Jones's analogy with the ink in a cube of water (Jones, 2008) we can see that in an anisotropic medium, the displacement profile can no longer be described by a sphere and is more accurately described by an ellipsoid with the long axis parallel to the long axis of the anisotropic medium. The axes of the *diffusion ellipsoid* are described as a principal long axis and two smaller ones which describe its width and depth. All three of these principal axes of this ellipsoid are perpendicular to each other and cross at the center point of the ellipsoid. They are called *eigenvectors* and the measures of their lengths (diffusion distance in a given time) *eigenvalues*, symbolized by the Greek letter λ.

The Eigensystem

The diffusion tensor formalism provides an 'internal reference frame' – the *eigensystem* (Jones, 2009). The tensor is called *diagonalized* when it is aligned with the principal axes of the measurement, since there is no correlation between displacements in orthogonal directions. In the diagonalized condition the diagonal elements of the tensor correspond to its eigenvalues. The three *eigenvalues, λ1, λ2 and λ3* correspond to the three diffusivities along the principal axes of the diffusion tensor and the orientation of the axes is given by the three eigenvectors which are mutually orthogonal. The tensor orientation lies parallel to the principal eigenvector, which is associated with the largest eigenvalue. This eigenvalue λ1 is also called the *longitudinal or axial diffusivity* and the two small axes which are perpendicular to the fiber will have lengths λ2 and λ3 (Song et al., 2002). These two minor axes are often averaged to obtain the *radial diffusivity* $(\lambda_2 + \lambda_3)/2$. This quantity seems to be a sensitive measure of degenerative pathology in some neurological conditions as it is an assessment of the degree of restriction due to membranes and other effects (e.g., Vaillancourt et al., 2009).

Diffusion tensor parameters

The commonly used DTI measures are *trace* and the anisotropy indices *fractional (FA) and relative anisotropy (RA*). Due to its usefulness for diagnosing vascular strokes in the brain by early detection of the *hypoxic edema,* trace-weighted images are currently the most clinically advantageous measure obtained from DTI (e.g., Sibon et al., 2009). It is defined as the sum of the three eigenvalues, and provides a rotationally invariant index of the overall amount of diffusivity with each image voxel. The trace divided by 3 – or the mean diffusivity – is a more commonly reported measure. It gives a measure of the bulk diffusivity ignoring directional preferences. The simplest anisotropy index would be the ratio of the largest to the smallest

eigenvalue. However, sorting the eigenvalues according to their magnitude introduces a bias in the measurements at low SNRs (Pierpaoli and Basser, 1996). To circumvent this problem, indices that do not require sorting (Pierpaoli and Basser, 1996) have been proposed and have shown to be less sensitive to the SNR. According to Pierpaoli and Basser (1996) the two most popular among these indices are the fractional (FA) and relative anisotropy (RA). Even though FA and RA are less sensitive to noise, they are still sensitive, so comparisons of these indices obtained from different studies using different imaging parameters should be approached with caution.

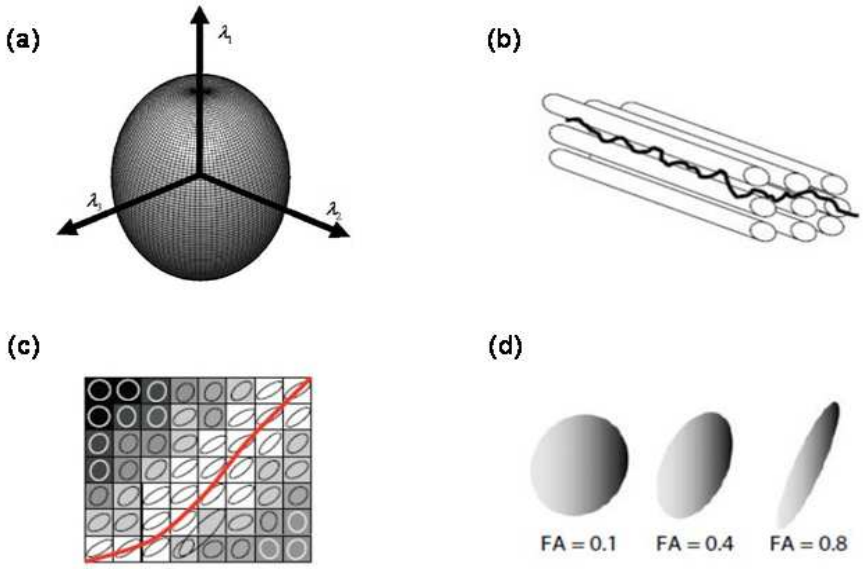


Figure 5.4: The diffusion tensor model (figure a,b,c adapted from Johansen-Berg and Behrens (2009), figure d adapted from Jones (2008)). Water diffusion at each voxel is modeled by a tensor, characterized by its three principal eigenvector and their associated eigenvalues λ1, λ2 and λ3 (a). These eigenvalues are used to calculate fractional anisotropy (FA) values which can range between zero and one and reflect the shape of the tensor: the more spherical the tensor, the lower the values (d). The diffusion of a water molecule (black line) within a bundle streamlining tractography proceeds by tracing a line through the tensor field, following the principal diffusion direction (b). The schematic shows a grid of voxels; the grayscale reflects FA (c).

Tensor orientation

By taking three diffusion-weighted images or ADC images – where the diffusion was measured along the three principal axes – it was possible to infer fiber orientation for the structures which were aligned with these three orthogonal axes. This knowledge led to the creation of fiber orientation maps based on ADC measurements (Douek et al., 1991; Nakada et al., 1994) which had the problem that they were rotationally variant i.e., they were dependent on the measured direction. A solution was provided by Jones et al. (1997) and Pierpaoli (1997)

where they showed that by using the information contained within the diffusion tensor or rather the principal eigenvector, robust fiber orientation maps could be derived. Orientation of the fibers can then be represented using different primary colors. In one of the most commonly used direction scheme, the x, y, and z components of the principal eigenvector are assigned to the red, green and blue channels of the video display, from which one can then gain an impression of the trajectory of the major white matter pathways (Pajevic and Pierpaoli, 1999).
Reconstructing white matter pathways in an automated way is the goal of *fiber tracking or tractography* (e.g., Conturo et al., 1999; Jones et al., 1999; Mori and Barker, 1999). Information derived from tensormap and tractography procedures can be used in the study of connective anatomy in health and disease, or utilized in region of interest (ROI) analyses within a specific anatomical structure or fiber system. Thus, the contrast provided by DTI proves the opportunity to integrate two neural properties that were unavailable prior to these recent advances – microstructural measures of tissue integrity and connectivity information for anatomically relevant measures of tissue integrity (Salat et al., 2009).

5.2.3 Fibertracking and its limitations

Originated in the late 1990s, the purpose of *fiber tracking or tractography* is to infer the 3-dimensional trajectories of anisotropic structures in tissue by piecing together discrete voxel-based estimates of the underlying continuous fiber orientation field (Basser and Pajevic, 2000; Jones et al., 1999; Mori and Barker, 1999).
Thereby it is of importance to differentiate two types of fiber tracking algorithms: deterministic and probabilistic.

- The underlying assumption of the *deterministic* approach (e.g., Mori and Barker, 1999) is that the principal eigenvector, i.e., the eigenvector associated with the largest eigenvalue is parallel to the underlying dominant fiber orientation in each voxel (Basser et al., 1994a, b) and forms a tangent to the space curve traced out by the white matter tract (Basser and Pajevic, 2000). The development of the space curve is performed by propagating a single pathway bi-directionally from a ‘seedpoint’ – which is usually the centre of an image voxel – by moving in a direction that is parallel to the main eigenvector. The underlying tensor field is assumed to be continuous and therefore as the step size is normally fixed, this approach requires sub-voxel estimates of the tensor which are obtained by interpolation (Conturo et al., 1999). This approach allows an estimate of the tensor field to be obtained at any arbitrary point within the imaged region.

  The fact that deterministic approaches only produce one reconstructed trajectory per seed

point, and hence branching of fasciculi will in general not be presented, is one of the criticisms against deterministic approaches. Furthermore, there is no indication of the confidence that one can assign to a reconstructed trajectory and the uncertainty associated with each main eigenvector estimate is non-uniform throughout the brain – with largest errors in the gray matter and the corticospinal fluid (Jones, 2003).

- *Probabilistic* algorithms work in general in the same way, but they propagate a large number of pathways from the seedpoint, instead of reconstructing just a single trajectory. On each stage of the evolving path, the direction in which to go next is drawn from a distribution of possible orientations. As result we get a set of multiple pathways passing through the seedpoint. This is then conventionally summarized by assigning to each voxel the percentage of pathways that pass through the voxel. Unlike in deterministic tracking where the stopping criteria for tracking is an arbitrary threshold on anisotropy in order to have a well defined eigenvector, the probabilistic algorithms usually do not have this kind of threshold in the termination criteria as they are not so dependent on a well defined principal eigenvector. Consequently trajectories from and into areas of low anisotropy such as gray matter are possible, and the only stopping criterion is the angular deviation between successive steps (e.g., Behrens et al., 2003).

  The result of the tracking process constitutes a map that tries to quantify how sure one can be that a pathway can be found between each voxel and the seedpoint. Probabilistic approaches usually produce one map per seedpoint, while deterministic tracking results are presented for a collection of seedpoints within an ROI. An important point in the interpretation of the probabilistic maps is that the maps represent likelihoods of connections through the data. The results are therefore strongly dependent on the quality of the data. A high likelihood of a connection does not mean that there is a white matter pathway to be found connecting two points in space. Hence, false positives and negatives are problematic in both, probabilistic and deterministic tracking methods. Another problem yet to be resolved in probabilistic tracking is the accumulated error problem. Since there is uncertainty in fiber orientation at each stage in the propagation of the tract, the error in fiber position will accumulate, and the longer the tract, the greater the error.

Besides the threat of ignoring the differentiation between the two selectable tracking algorithms and neglecting the specific properties and its corresponding limitations, one has to take note of the fact that during the modeling process the tensor model cannot adequately characterize fiber orientation when there is more than one fiber population within a voxel. The Gaussian tensor model assumes the principal eigenvector to be co-aligned with the dominant

fiber orientation within a voxel; hence a single fiber orientation is insufficient to completely characterize the fiber orientations in regions which have multiple fiber populations. Alternative techniques have been able to estimate multiple dominant diffusion orientations within the same imaging voxel and suggest that they correspond to multiple fiber populations (Assaf and Basser, 2005; Tournier et al., 2004; Tuch et al., 2002). And attempts have been made to include such complex fiber information into both deterministic (Hagmann et al., 2003) and probabilistic (Hosey et al., 2005; Parker and Alexander, 2005) tractography techniques.

5.2.4 DTI in the field of aphasia

The most prominent fiber tract associated with language function which is most frequently studied is the *arcuate fasciculus (AF).* Studies which examined the AF in healthy subjects were interested in the anatomical location (Hong et al., 2009) or examined the asymmetry and lateralization respectively, of the fiber tract (Glasser and Rilling, 2008; Lebel and Beaulieu, 2009; Propper et al., 2010). Lebel and Beaulieu (2009) even linked the lateralization to different stages of development and related it to cognitive functions in children. The AF in healthy subjects was as well studied in a group around Catani who embedded their study into the background of the classical disconnection model of language (Wernicke-Geschwind) and tried to reassess the anatomy of the AF and the connectivity of perisylvian language areas using modern DTI methods (Catani et al., 2005). Furthermore, they showed that the classical Wernicke and Broca's region is not only connected by a direct pathway – the 'classical' AF –, but furthermore two indirect pathways connecting the two regions via the inferior parietal lobule or Geschwind's territory. Gharabaghi et al. (2009) have in turn identified the same subdivision of the AF on the right hemisphere. Since the AF is historically mainly associated with conduction aphasia, several studies have examined this relationship and either associated it with the Wernicke-Geschwind Model (Anderson et al., 1999; Zhang et al., 2009) or proposed a new language network model emphasizing that the AF connects posterior brain areas with Broca's area via a relay station in the premotor/motor areas (Bernal and Ardila, 2009). The knowledge of the anatomic basis of aphasia after stroke has both theoretic and clinical implications by informing models of cortical connectivity and providing data for diagnosis and prognosis. To date there are only a few studies which use DTI to address the relationship between damage to specific white matter tracts and linguistic deficits after left hemisphere stroke. One of them found lower FA values in the SLF/AF in the left hemisphere of stroke patients, which indicated a greater damage to these tracts (Breier et al., 2008). Furthermore, Breier et al. (2008) found a significant correlation with decreased ability to repeat spoken lan-

guage. FA values as well as number of fibers were used in another study where the predictive value of DTI in acute stroke patients was assessed (Hosomi et al., 2009). Hereby Hosomi et al. (2009) found a loss of leftward asymmetry in number of fibers to predict aphasia. Schlaug et al. (2009) likewise used the measure of fiber numbers in their study, comparing six patients from pre to post Melodic Intonation Therapy (MIT) treatment. The number of fibers increased significantly post compared to pre treatment; however, the correlation with a behavioral measure did not reach significance due to the small subject group (Schlaug et al., 2009). To date there are hardly any studies which examine other language fiber tracts than the AF, e.g., the *uncinate fasciculus (UF)* or the *extreme capsule fiber system (EmC).* An exception is a study conducted by Duffau et al. (2009), in which they evaluate the necessity of the UF for languageMost recent studies implemented all the three language tracts into *Hickok and Peoppel's dual stream model of auditory language processing*. In this model (Hickok and Poeppel, 2004) the AF serves the dorsal stream which is involved in auditory-motor integration by mapping acoustic speech sounds to articulatory representations while the UF and the EmC constitute the ventral stream which serves as a sound to meaning interface by mapping sound-based representations of speech to widely distributed conceptual representations (Duffau, 2008; Frey et al., 2008; Friederici, 2009; Parker et al., 2005; Saur et al., 2008).

II Empirical Part

6 Studies

The four studies presented in this dissertation aimed at investigating the efficacy of Melodic Intonation Therapy (MIT) in an open-label pilot clinical trial. Patient's language abilities were assessed at 5 different timepoints during the course of an intensive 15-week therapy in order to evaluate improvements in propositional speech and possible effects of generalization to unpracticed words and phrases. In the first (chapter 6.1) and the second study (chapter 6.2) functional magnetic resonance imaging (fMRI) was used in order to determine the neural treatment effect and the reorganization or plastic changes in the brain. Large left-hemisphere lesions that extend into the deep white matter left most of the patients with partially or fully damaged white matter fiber tracts which belong to the language network. We hypothesized that this loss would be compensated for by the language network on the right hemisphere. Using diffusion tensor imaging (DTI), changes in the structure of the white matter on the right hemisphere comparing pre with post therapy were investigated in the third study (chapter 6.3). Furthermore, in the fourth study (chapter 6.4) we created a new variable lesionload which combines the lesionmaps of patients with canonical fiber tracts derived from healthy subjects in order to assess the extent of the damage and to predict speech outcome.

6.1 Study 1: From Singing to Speaking: Why Singing May Lead to Recovery of Expressive Language Function in Patients with Broca's Aphasia

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Abstract

It has been reported that patients with severly nonfluent aphasia are better at singing lyrics than speaking the same words. This observation inspired the development of Melodic Intonation Therapy (MIT), a treatment whose effects have been shown, but whose efficacy is unproven and neural correlates remain unidentified. Because of its potential to engage/unmask language-capable regions in the unaffected right hemisphere, MIT is particularly well suited for patients with large left hemisphere lesions. Using two patients with similar impairments and stroke size/location, we show the effects of MIT and a control intervention. Both interventions' post-treatment outcomes revealed significant improvement in propositional speech that generalized to unpracticed words and phrases; however, the MIT-treated patient's gains surpassed those of the control- treated patient. Treatment-associated imaging changes indicate that MIT's unique engagement of the right hemisphere, both through singing and tapping with the left hand to prime the sensorimotor and premotor cor- tices for articulation, accounts for its effect over nonintoned speech therapy.

Introduction

Of the estimated 600,000-750,000 new strokes occurring in the US each year (according to data presented by the American Heart Association and the National Institutes of Health) [17] approximately 20% result in some form of aphasia. Aphasia is a condition characterized by either partial or total loss of the ability to communicate verbally. A person with aphasia may have difficulty speaking, reading, writing, recognizing the names of objects, and/or understanding what other people have said. Aphasia, a disorder caused by a brain injury (e.g., stroke, tumor, or trauma), can be subdivided into fluent and nonfluent categories. Nonfluent aphasia (as in the patients to be discussed here) generally results from lesions in the frontal lobe including the portion of the left frontal lobe known as Broca's region. Named for Paul Broca (1864), who first associated this area of the brain with nonfluent aphasia, this region is thought to consist of the posterior inferior frontal gyrus (IFG) encompassing Brodmann's areas 44 and 45. However, subsequent reports have shown that a wider array of lesions in the frontal lobes and in subcortical brain structures can also present a clinical picture of a Broca's aphasia (see Kertesz, Lesk, & McCabe, 1977).

Surprisingly, there are no universally accepted methods for the treatment of nonfluent aphasia against which new or existing interventions can be tested, nor have any criteria been established for determining treatment efficacy. Most interventions in the subacute phase are conducted by speech therapists who evaluate patients' individual needs, then use a combination of techniques to help recover language/facilitate communication. Despite the lack of specific criterion for success, most therapists would agree that treatment efficacy would be defined by patients' ability to show improvement in speech output that generalizes to untrained language structures and/or contexts (Thompson & Shapiro, 2007).

Because the neural processes that underlie post stroke language recovery remain largely unknown, it has not been possible to effectively target them using specific therapies. To date, functional imaging (mostly positron emission tomography) of language recovery has largely focused on spontaneous recovery, and patients have been imaged only after natural recovery has run its course (Warburton, Price, Swinburn, & Price, 1999; Weiller et al., 1995). Some studies emphasize the role of preserved language function in the left hemisphere (Cappa & Vallar, 1992; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999), while others propose that language function is restored when right-hemisphere regions compensate for the loss (Basso, 1989; Blasi, Young, Tansy, Petersen, Snyder, & Corbetta, 2002; Cappa & Vallar, 1992;

[17] http://www.wrongdiagnosis.com/artic/ninds_aphasia_information_page_ninds.htm

Cappa et al., 1997; Kinsbourne, 1998; Moore, 1989; Selnes, 1999; Weiller et al., 1995). Still other studies report evidence for bihemispheric language processing (Heiss & Thiel, 2006; Mimura, Kato, Sano, Kojima, Naeser, & Kashima, 1998; Rosen et al., 2000; Saur et al., 2006; Winhuisen et al., 2005). Interestingly, only a few studies have examined the neural correlates of an aphasia treatment by contrasting pre- and post-therapy assessments (Cornelissen, Laine, Tarkiainen, Järvensivu, Martin, & Salmelin, 2003; Musso, Weiller, Kiebel, Muller, Bulau, & Rijntjes, 1999; Saur et al., 2006; Small, Flores, & Noll, 1998; Thompson & Shapiro, 2005). The general consensus is that there are two routes to recovery. In patients with small lesions, there tends to be more activation of left hemisphere perilesional cortex and variable right hemisphere activation during the recovery process or after recovery. In patients with large left-hemisphere lesions that involve language regions in the fronto-temporal lobes, there tends to be more activation of the homologous language-capable regions in the right hemisphere.

Assuming that potential facilitators of language recovery may be either undamaged portions of the left- hemisphere language network, language-capable regions in the right hemisphere, or both, it is necessary to explore treatments that can better engage these regions and ultimately, change the course of natural recovery through neural reorganization. One therapy capable of engaging regions in both hemispheres is Melodic Intonation Therapy (MIT; Albert, Sparks, & Helm, 1973; Sparks, Helm, & Albert, 1974), a method developed in response to the observation that severely aphasic patients can often produce well articulated, linguistically accurate words while singing, but not during speech (Gerstman, 1964; Geschwind, 1971; Hebert, Racette, Gagnon, & Peretz, 2003; Keith & Aronson, 1975; Kinsella, Prior, & Murray, 1988). MIT is a hierarchically structured treatment that uses intoned (sung) patterns to exaggerate the normal melodic content of speech at three levels of difficulty. The intonation works by translating prosodic speech patterns (sung phrases) using just two pitches. The higher pitches represent the syllables that would naturally be stressed (accented) during speech (see Figure 1).

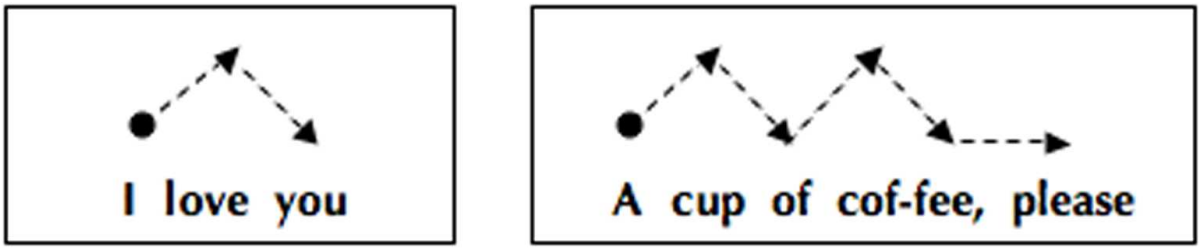

Figure 1: Spoken phrases (prosodic patterns) transposed into melodic intonation patterns. Pitches are determined by the natural prosody of speech-accented syllables are presented on the higher of the two pitches.

At the simplest level, patients learn to intone (sing) a series of 2-syllable words/phrases (e.g., "Water," "Ice cream," "Bathroom") or simple, 2- or 3-syllable social phrases (e.g., "Thank you," "I love you"). As each level is mastered, patients move to the next, and phrases gradually increase in length (e.g., "I am thirsty," "A cup of coffee, please"). Beyond the increased phrase length, the primary change from level to level of MIT lies in the way the treatment is administered and the degree of support that is provided by the therapist.

MIT contains two unique elements that set it apart from other, non-intonation-based therapies: (1) the melodic intonation (singing) with its inherent continuous voicing, and (2) the rhythmic tapping of each syllable (using the patient's left hand) while phrases are intoned and repeated. Since the initial account of its successful use in three chronic, nonfluent (Broca's) aphasic patients (Albert, Sparks, & Helm, 1973), reports have outlined a comprehensive program of MIT (Helm-Estabrooks & Albert, 1991; Sparks & Holland, 1976) including strict patient selection criteria (Helm-Estabrooks, Nicholas, & Morgan, 1989), and data that showed significant improvement on the Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983) after treatment (Bonakdarpour, Eftekharzadeh, & Ashayeri, 2000; Sparks, Helm, & Albert, 1974). In a case study comparing MIT to a non-melodic control therapy, Wilson, Parsons, and Reutens (2006) found that MIT had a general facilitating effect on articulation, and a longer-term effect on phrase production that they attributed specifically to its melodic component. However, the outcomes of that study were measured by the patient's ability to produce practiced phrases prompted by the therapist, rather than by the transfer of language skills to untrained structures and/or contexts.

Another important characteristic of MIT is that, unlike many therapies administered in the chronic phase that involve one to two short sessions per week, MIT engages patients in intensive treatment totaling 1.5 hrs/day, five days/week until the patient has mastered all three levels of MIT. In addition to its unique elements, there are several other components that play an important role in MIT, but are also used by other therapies, among them are the slow rate of vocalization (one syllable/s) and an administration protocol that includes one-on-one sessions with a therapist who introduces and practices words/phrases using picture cues while giving continuous feedback. These shared features were carefully considered as we designed a control intervention for MIT that included the elements common to other therapies while specifically excluding the melodic intonation/continuous voicing and rhythmic tapping that may likely be the key factors in its effectiveness. The original interpretation of MIT's path to successful recovery was that it engaged expressive language areas in the right hemisphere (Albert et al., 1973; Sparks et al., 1974), although to date, this has not yet been proven. Alternatively

MIT may exert its effect by either unmasking existing music/language connections in both hemispheres, or by engaging preserved language-capable regions in either or both hemispheres. Since MIT incorporates both melodic and rhythmic aspects of music (Albert et al., 1973; Boucher, Garcia, Fleurant, & Paradis, 2001; Cohen & Masse, 1993; Helm-Estabrooks & Albert, 1991; Sparks & Holland, 1976), it may be unique in its potential ability to engage both hemispheres. Belin et al. (1996) suggested that MIT-facilitated recovery was associated with the reactivation of left-hemisphere regions, most notably the left pre- frontal cortex, just anterior to Broca's region. Although, this publication was the first to examine patients treated with an MIT-like intervention using functional neuroimaging, their findings were both surprising and somewhat contrary to the hypotheses proposed by the developers of MIT (Albert et al., 1973; Sparks et al., 1974). Furthermore, to help interpret Belin and colleagues' findings it is important to consider the following: First, only two of their seven patients had Broca's aphasia; the rest were diagnosed with global aphasia. Second, they conducted only one imaging session, which took place after therapy (no pre-/post-comparison). And finally, their analysis was done in predefined regions of interest rather than across the entire brain space. It is interesting to note that although Belin and colleagues' primary finding was an activation of left prefrontal regions when participants were asked to repeat intoned words, there is an important aspect of their study that is not often reported. In their analysis comparing the repetition of spoken words with the hearing of those words, they found blood flow changes that occurred predominantly in the right hemisphere (including the right temporal lobe and the right central operculum), which concurs with some of our findings detailed below.

The aim of our study is to describe and discuss the unique and shared elements of MIT and to contrast the behavioral and neural treatment effects of MIT with a control intervention, Speech Repetition Therapy (SRT), in two prototypical patients.

Methods

Participants

We present two of the patients we have treated to date in our ongoing study of MIT's effects. Both were diagnosed with severe nonfluent aphasia (restricted verbal output, impaired naming and repetition, relatively unimpaired comprehension) as the result of a left-hemisphere ischemic stroke involving mainly the superior division of the middle cerebral artery, and classified as having Broca's aphasia. Despite the fact that the patients had already received more than one year of traditional speech therapy prior to enrollment in our study, they presented with significantly impaired verbal output and remained unable to speak fluently. Both patients

were tested twice prior to therapy to establish a stable baseline. In addition, we assessed their ability to speak/sing the lyrics of familiar songs by analyzing the number of Correct Information Units (CIUs; correct, meaningful words) that each patient produced while singing and speaking compared to the total number of words for at least two familiar songs. Patient #1 (male; age 47; right-handed; native language English; 12+ years of schooling; 2-3 years of instrumental practice as a child; no active singing in a choir; moderate to severe right hemiparesis; independent in activities of daily living, ADL; Barthel-index of 95 out of 100) underwent an intensive course of MIT and was assessed on behavioral and neural measures at a series of regular intervals that included assessments after 40 and 75 sessions of MIT. Patient #2, (male; age 58; right-handed; native language English; 12+ years of schooling; 1-2 years of instrumental practice as a child and some singing in choirs in high school and college; moderate to severe right hemiparesis; independent in activities of daily living, ADL; Barthel-Index of 95 out of 100), matched to Patient #1 with regard to lesion size/location and baseline speech production abilities, underwent an equally intensive alternative intervention, SRT, designed to control for the elements of MIT that are common to other speech therapies, and exclude its distinct features, the melodic intonation and rhythmic tapping with the left hand.

After undergoing 40 sessions of SRT and the same series of behavioral and neural assessments administered to Patient #1, Patient #2 underwent treatment with MIT and was assessed after 40 and 75 therapy sessions. Thus, both patients had behavioral and brain imaging assessments before and after therapy. The proportion of spoken CIUs/total words possible was significantly lower than the proportion of sung CIUs/total words in both patients. Although both patients actually received 75 ses- sions of MIT, the comparison between the two interventions reported here was made after each patient had received 40 sessions of their originally assigned treat- ment (MIT and SRT respectively).

Language Assessments

Based on their Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983) scores, both patients were classified as having Broca's aphasia. Patients underwent a series of language assessments (see below) at baseline, and again, four weeks later. This was done in order to establish a stable baseline and record any fluctuations in performance. The same set of tests was administered to both patients after 40 treatment sessions (post40). Further assessments were done after 75 sessions (post75). The test battery consisted of the following speech production measures designed to quantitatively assess spontaneous speech: (1) Conversational interview: regarding patients' biographical data, medical history, post-stroke treatment, daily activities, etc.; and (2) Descriptions of complex pictures: using patients' re-

sponses on these measures, we calculated the average number of CIUs/min and the average number of syllables/phrase. All meaningless utterances, inappropriate exclamations, incorrect responses (inaccurate information), and/or perseverations were excluded prior to scoring. Participants were also given confrontational picture naming tasks, including the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2001) and a matched subset (30 images) of the Snodgrass-Vanderwart color pictures (1980). All behavioral assessments were videotaped for analysis. Videotapes were transcribed and patients' speech output was checked for intelligibility, then scored by an independent researcher who was not associated with the patients during therapy.

Experimental Stimuli and fMRI Paradigm

A list of 16 bisyllabic words/phrases that both patients were capable of saying at baseline were used for stimuli in the fMRI experimental task at all imaging time points, and the rate of speaking/singing (one syllable/sremained constant throughout the study. The functional task consisted of five conditions: two experimental (spoken or sung bisyllabic words/phrases) and three control (humming, phonation, and silence). In the experimental conditions, participants heard an investigator saying/ singing two-syllable words or phrases (presented at the rate of one syllable/s), then repeated exactly what they had heard after an auditory cue. In the silence condition, participants were asked to wait for the cue, then take a breath as if to respond as they had in the other conditions (for more details on the fMRI tasks see Ozdemir, Norton, & Schlaug, 2006). Functional magnetic resonance imaging (fMRI) and sparse temporal sampling was done as previously reported in detail (see Gaab, Gaser, Zaehle, Chen, & Schlaug, 2003, and Ozdemir, Norton, & Schlaug, 2006). Participants' responses were recorded for offline analysis. Both of the patients reported here had 100% correct response rates.

Treatments

The two patients in this study were randomly assigned to treatment type (either MIT or SRT). Both patients worked one-on-one with the same therapist for 1.5 hours/day, five days/week, and were given a set of materials for daily home practice. Both interventions were identical with regard to the length of phrases, the use of picture stimuli, and the level of support provided by the therapist at each stage of advancement. SRT differed only in that the phrases were spoken rather than intoned (sung), syllables were not sustained, and there was no hand tapping associated with the production of speech.

Results

Behavioral and Imaging Effects of the MIT Intervention

Patient #1, who was 13 months post onset of a left-hemispheric stroke (see Figure 2 for lesion location/size), was assigned to treatment with MIT. He underwent two pre-treatment assessments separated by 4 weeks (pre1 and pre2), a mid-treatment assessment after 40 therapy sessions (post40), and a post-treatment assessment after 75 sessions of MIT (post75).

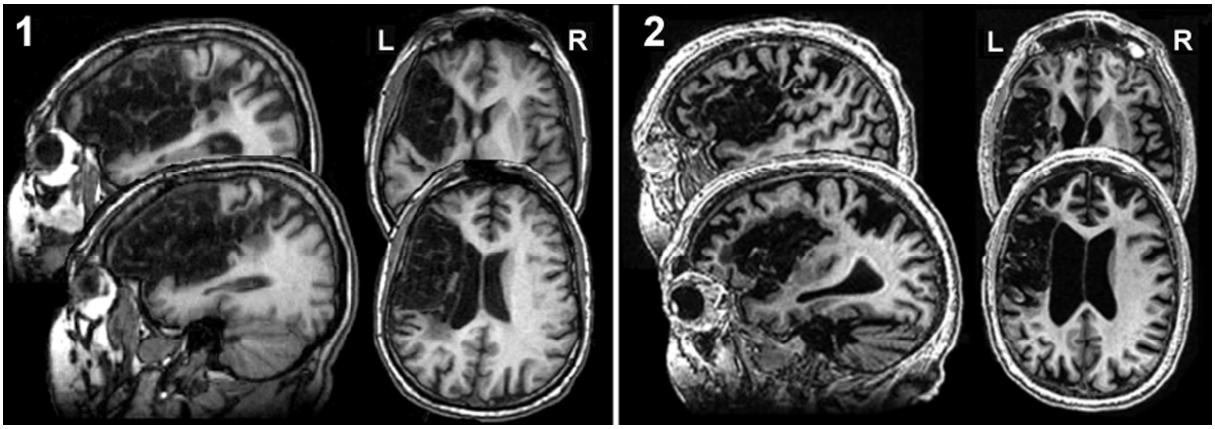

Figure 2: High-resolution, T1-weighted images show the chronic, left-hemisphere lesion location and extent of Patients #1 and #2, encompassing both Broca's region and the anterior part of the superior temporal lobe.

At baseline, his spontaneous speech assessments yielded results consistent with his diagnosis. Repeat assessments conducted prior to MIT showed no significant changes. After only 40 sessions of MIT, he showed significant improvement on measures of speech output and confrontational naming, and after 75 sessions of MIT, those improvements were even more pronounced (for all behavioral results, see Table 1).

ID	Treatment	Measure	Baseline	Post40	% Change	Post75	% Change
Patient 1	MIT	CIUs/min.	**4.40**	**10.10**	*229.50*	**13.90**	*315.90*
		Syllables/phrase	**1.80**	**4.10**	*227.80*	**4.70**	*261.10*
		Picture naming (% correct)	**60.00**	**80.00**	*133.30*	**95.00**	*158.30*
Patient 2	SRT	CIUs/min.	**3.60**	**6.80**	*188.90*		
		Syllables/phrase	**2.40**	**4.00**	*166.70*		
		Picture naming (% correct)	**59.00**	**72.00**	*122.00*		
Patient 2	MIT (after SRT)	CIUs/min.	**6.80**	**16.70**	*245.60*	**20.50**	*301.50*
		Syllables/phrase	**4.00**	**8.90**	*222.50*	**10.10**	*252.50*
		Picture naming (% correct)	**72.00**	**90.00**	*125.00*	**89.00**	*123.60*

Table 1: Summary of Language Outcomes.

Note: MIT = Melodic Intonation Therapy; SRT = Speech Repetition Therapy; CIU/min = Correct Information Units/min; Picture naming = percent of correctly named pictures out of 60 (Boston Naming Test); Post40 refers to assessment after 40 treatment sessions; Post75 = after 75 treatment sessions.

Patient #1's baseline and post40 fMRI studies (see Figure 3) showed posterior perisylvian activation on the left, and both superior temporal and inferior precentral gyrus activation on the right during the speaking condition (speaking vs. silence contrast); however, the post40 scan also showed more prominent right-hemispheric activation involving the right posterior middle premotor cortex and right inferior frontal gyrus, as well as a slightly smaller increase in activation of the posterior superior temporal gyrus.

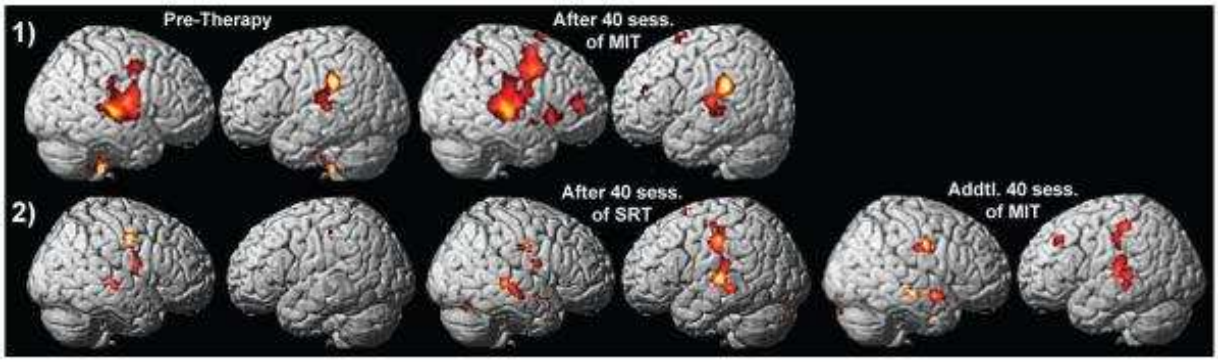

Figure 3: fMRI activation maps (superimposed onto the surface of a spatially standardized normal brain) of the contrast „overt speaking vs. silence (control condition)" ($p<0.05$ FWE) for patients #1 and #2 at baseline and after 40 therapy sessions. The color coding reflects different magnitudes of activation: the color yellow reflects a stronger activation than the color red. Patient #2 also shows the "overt speaking vs. Silence (control condition)" contrast after an additional 40 sessions of MIT that followed the SRT sessions. Slight differences can be seen in the regional magnitude of activation with a greater magnitude of activation in the right premotor/motor and temporal lobes (yellow level of activation) and the slightly lower magnitude of activation in the left posterior perisylvian region (more red than yellow) comparing the images after MIT with the images afer SRT treatment for Patient #2.

Behavioral and Imaging Effects of the SRT Intervention

Patient #2, who was 12 months post onset of a left- hemispheric stroke (see Figure 2 for lesion location/ size), was assigned to treatment with SRT. His dissociation between speaking and singing and baseline speech production rate were similar to that of Patient #1. There were no significant changes on repeat baseline assessments. After 40 SRT sessions, Patient #2's speech production scores improved, his picture-naming score increased (Table 1), and his fMRI studies (Figure 3 in color plate section) that had at baseline shown activation of the posterior superior temporal gyrus (STG), superior temporal sulcus (STS), and middle to inferior precentral gyrus on the right, with a very small area of activation on the left during the speaking condition (Overt Speaking vs. Silence control condition), showed more prominent left-hemispheric activation involving the inferior part of the pre- and post-central gyrus, as well as the middle and posterior portions of the STG/STS, left more than right. Patient #2 also shows the Overt Speaking vs. Silence (control condition) contrast after an additional 40 sessions of

MIT that followed the SRT sessions. Slight differences can be seen in the regional magnitude of activation, with a greater emphasis on the right premotor/motor and temporal lobes (yellow level of activation) and the slightly lower magnitude of activation in the left posterior perisylvian region (more red than yellow) comparing the images after MIT with the images after SRT treatment for Patient #2. The between-treatments comparison (Patient #1 MIT vs. Patient #2 SRT) made after 40 sessions (see also Table 1) showed that the MIT-treated patient had greater improvement on all outcomes than the SRT-treated patient. fMRI studies revealed that Patient #1 showed significant fMRI changes in a right-hemisphere network involving the premotor, inferior frontal, and temporal lobes, while Patient #2 had changes in a left-hemisphere network consisting of the inferior pre- and post-central gyrus and the superior temporal gyrus. Following his post40-SRT assessment, Patient #2 was enrolled in the MIT treatment, and the post40 scores became the new baseline from which the effects of MIT would be measured. After 40 sessions of MIT, Patient #2 showed a further increase in speech output and picture-naming, and his post75-MIT assessments revealed further gains in speech output while the picture-naming score remained stable (see Table1).

Discussion

The traditional explanation for the dissociation between speaking and singing in aphasic patients is the presence of two routes for word articulation: one for spoken words through the brain's left hemisphere, and a separate route for sung words that uses either the right or both hemispheres. The small amount of empirical data available supports a bihemispheric role in the execution and sensorimotor control of vocal production for both speaking and singing (Bohland & Guenther, 2006; Brown, Martinez, Hodges, Fox, & Parsons, 2004; Guenther, Hampson, & Johnson, 1998; Jeffries, Fritz, & Braun, 2003; Ozdemir et al., 2006), with a tendency for greater left-lateralization for speaking under normal physiological conditions (i.e., faster rates of production during speaking than singing). The representation of sensory elements of music and language might be either separate, or in different locations with smaller degrees of overlap (for more details on this see also Koelsch, Fritz, Schulze, Alsop, & Schlaug, 2005; Koelsch, Gunter, von Cramon, Zysset, Lohmann, & Friederici, 2002; Patel, 2003; Peretz, 2003). Nevertheless, if there is a bihemispheric representation for speech production, then the question of why an intervention that uses singing or a form of singing such as MIT has the potential to facilitate syllable and word production, still remains. In theory, there are four possible mechanisms by which MIT's facilitating effect may be achieved: (1) Reduction of speed: in singing, words can be articulated at a slower rate than in speaking,

thereby reducing dependence on the left-hemisphere; (2) Syllable lengthening: provides the opportunity to distinguish the individual phonemes that together form words and phrases. Such connected segmentation, coupled with the reduction of speed in singing, can help nonfluent aphasic patients become more fluent, and may receive greater support from right-hemisphere structures; (3) Syllable "chunking": prosodic features such as intonation, change in pitch, and syllabic stress may help patients group syllables into words and words into phrases, and this "chunking" (Chase & Simon, 1973; de Groot, 1965) may also enlist more right-hemi- sphere support; and 4) Hand tapping: it is likely that MIT engages a right-hemispheric, sensorimotor network through the tapping of the patient's left hand as each syllable is sung (one tap/syllable, one syllable/s), which may in turn provide an impulse for verbal production in much the same way that a metronome has been shown to serve as a "pacemaker" in other motor activities (rhythmic anticipation, rhythmic entrainment; Thaut, Kenyon, Schauer, & McIntosh,1999). In addition, there may be a set of shared neural correlates that control both hand move- ments and articulatory movements (Gentilucci, Benuzzi, Bertolani, Daprati, & Gangittano, 2000; Meister, Boroo- jerdi, Foltys, Sparing, Huber, & Topper, 2003; Tokimura, Tokimura, Oliviero, Asakura, & Rothwell, 1996; Uozumi, Tamagawa, Hashimoto, & Tsuji, 2004), and further, the sound produced by the tapping may encourage auditory-motor coupling (Lahav, Saltzman, & Schlaug, 2007).

The two unique elements of MIT most likely to make the strongest contribution to the therapy's beneficial effects are the melodic intonation with its inherent sustained vocalization, and tapping with the left hand. How might melodic intonation influence recovery? Functional imaging tasks targeting the perception of musical components that require a more global than local processing strategy (e.g., melodic contour, musical phrasing, and/or meter) tend to elicit greater activity in right-hemispheric brain regions than in left-hemispheric regions. It has been shown that tasks that emphasize spectral information over temporal information have shown more right- than left-hemispheric activation (Zatorre & Belin, 2001). Similarly, patients with right-hemisphere lesions have greater difficulty with global processing (e.g., melody and contour processing) than those with left-hemisphere lesions (Peretz, 1990; Schuppert, Munte, Wieringa, & Altenmueller, 2000). It is most likely that the two unique elements of MIT, the melodic intonation with its inherent sustained vocalization and the rhythmic tapping of the left hand, make the strongest contribution to the therapy's beneficial effect.

The effects of the left hand tapping should be considered in the same context. Once the right temporal lobe is specifically engaged by the melodic intonation and melodic contour, it is conceivable that the role of the left hand tapping could be the activation and priming of a

right-hemispheric sensorimotor network for articulation. Since concurrent speech and hand use occurs in daily life, and gestures are frequently used during speech, hand movements, possibly in synchrony with articulatory movements, may have a facilitating effect on speech production, but the precise role of this facilitation is unknown. We hypothesize that tapping the left hand may engage a right-hemispheric sensorimotor network that coordinates not only hand movements but orofacial and articulatory movements as well. There is some evidence in the literature that such superordinate centers exist in the premotor cortex and share neural substrates for hand and orofacial movements (Meister et al., 2003; Tokimura et al., 1996; Uozumi et al., 2004). Furthermore, behavioral (Gentilucci et al.,2000), neurophysiological (Meister et al., 2003; Tokimura et al., 1996) and fMRI studies (Aziz-Zadeh, Wilson, Rizzolatti, & Iacoboni, 2006) have shown that motor and linguistic cortical representations of objects are closely linked, and that the premotor cortex may belong to an integrative network coordinating motor and linguistic expression. An additional or alternative explanation is that the left hand tapping may serve the same function as a pacemaker or metronome has in rehabilitation of other motor activities, and in so doing, may facilitate speech production through rhythmic anticipation, rhythmic entrainment, or auditory-motor coupling (see also Lahav et al., 2007, and Thaut et al., 1999).

In summary, the melodic intonation and left hand tapping are the critical, unique elements of MIT that may likely be responsible for its therapeutic effect and might explain the predominant right hemispheric activation pattern seen in our prototypical patient. Elements of MIT that are shared with other, non-intonation-based therapies (e.g., the intensity of the intervention, direct therapist/patient interaction, unison and antiphonal repetition of words and phrases) also have therapeutic effects, as can be seen in our patient treated with SRT. Although caution should be exercised when making generalizations from results in two prototypical patients, we hope that our findings will serve as a source for fur- ther discussion on the efficacy of MIT, the neural correlates of MIT, and the choice of appropriate control interventions for MIT.

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6.2 Study 2: From Singing to Speaking: Behavioral and Neural Correlates of Intensive Treatment with Melodic Intonation Therapy

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Abstract

Patients with large left hemisphere lesions and post-stroke aphasia often stay non-fluent despite intensive traditional speech therapy. Melodic Intonation Therapy (MIT), a therapy that was based on the clinical observation of aphasic patient's ability to sing lyrics but not speak the same words, has been claimed to have the potential to facilitate recovery in these nonfluent patients with large left hemisphere strokes, although proof of this claim is difficult to come by. In an open-label proof-of-concept trial, we found significant improvements in a measure of propositional speech and found evidence that the improvement generalized to unpracticed words and phrases. Baseline variations prior to therapy were minimal and repeat post-treatment assessments showed that this group of chronic nonfluent aphasic patients maintained their speech output improvement. Treatment-associated imaging changes were seen in a right-hemisphere network that included the superior temporal gyrus, the primary sensorimotor, premotor, posterior inferior frontal cortex, the pre-supplementary motor region, and the supramarginal gyrus, with most regions connected via the arcuate fasciculus. Of all those regions, only imaging changes in the posterior IFG region are correlated with improvements in speech output. Our data suggest that MIT can lead to persistent gains in speech output in chronic non-fluent patients, and that changes in a right hemispheric network of brain regions, in particular in the right posterior IFG are related to the improvements**.**

Introduction

Patients with large left-hemispheric lesions and resulting post-stroke aphasia are typically nonfluent and may have impaired comprehension if their lesion pattern involves the entire middle cerebral artery territory. Compared to patients with smaller lesions, these patients do not show a good natural recovery rate, and do not appear to be as responsive to traditional speech-therapy (Kertesz et al 1977; Pedersen et al 1995; Pedersen et al 2004; Rosen et al 2000; Schlaug et al 2010b; Wade et al 1986). Most language interventions used in the sub-acute and chronic stroke phases are administered by speech therapists who evaluate patients' individual needs, then use a combination of techniques tailored to the particular patient's impairment profile. To date, there are no universally accepted interventions or "gold-standards" for the treatment of severe nonfluent aphasias against which new or existing unconventional interventions can be compared to, nor is there agreement in the literature on criteria for measuring meaningful treatment efficacy. Nevertheless, most therapists, clinicians, and researchers in the aphasia field would probably agree that a treatment can be considered effective if patients are able to show improvements in speech output that generalizes to untrained language structures and/or contexts (Thompson & Shapiro 2007). While a meta-analysis by Robey (1998) determined that an array of treatment methods for aphasia is, on average, beneficial, effect sizes varied widely (Moss & Nicholas 2006; Robey 1998). Some of this variability is undoubtedly due to the differences in treatment approaches used across studies and other measures that are known to affect stroke outcome and recovery potential such as age, lesion volume, sex (Lazar & Antoniello 2008), lesion load of relevant language structures (Marchina et al 2011), and factors such as degree of hemispheric language laterality, anatomical development of the right auditory-motor white matter tracts (e.g., arcuate fasciculus), the degree of inter-hemispheric connectivity of speech-motor regions and small vessel ischemic lesion burden. However, their significance as predictors of recovery has not yet been examined in large scale studies. Furthermore, the results of a meta-analysis (Bhogal et al 2003) led to the conclusion that experimental aphasia treatments are more likely to achieve positive results if the total amount of therapy exceeds 55 hours.

Neuroimaging studies have increased our knowledge of recovery processes and reorganization of language functions in the post-stroke period, mostly examining natural outcome or the effects of traditional speech therapy. Some of these studies emphasize the role of the preserved language function in the left hemisphere (Heiss & Thiel 2006; Meinzer et al., 2004 & 2008), while others suggest that language functions improve when regions in the right hemisphere compensate for the left-hemisphere impairment (Crosson et al 2005; Musso et al 1999;

Raboyeau et al 2008; Richter et al 2008). Yet other studies yield evidence for bi-hemispheric language processing or more transient right hemisphere activation after a left hemisphere stroke (Menke et al 2009; Pulvermuller et al 2005; Saur et al 2006). To date only a few studies have examined the neural correlates of treatment by contrasting post- versus pre-therapy assessment (Cherney & Small 2006; Meinzer et al 2007; Meinzer et al 2008; Vitali et al 2007). Despite some heterogeneity in the findings and patient populations in these studies, there seems to be a general consensus that there are two routes to recovery. In right-handed patients with small left hemisphere lesions and typically a milder form of aphasia, there tends to be recruitment of perilesional cortex on the left and variable involvement of right-hemisphere homologous language regions during the recovery process (Fridriksson et al 2012; Heiss et al 1999; Heiss & Thiel 2006; Hillis 2007; Rosen et al 2000). In right-handed patients with large left hemisphere lesions involving a large proportion if not all language-related regions of the fronto-temporal lobes, the only path to recovery may be through recruitment of homologous language and speech-motor regions in the right hemisphere (Rosen et al 2000; Schlaug et al 2008). It has been suggested that recovery via the right hemisphere may be less efficient than recovery via the left hemisphere (Heiss et al 1999; Heiss & Thiel 2006), possibly because patients with relatively large left hemispheric lesions are generally more impaired and recover to a lesser degree than patients with smaller left hemisphere lesions. Nevertheless, activation of right-hemisphere regions during speech/language fMRI tasks has been reported in patients with aphasia, irrespective of their lesion size (Rosen et al 2000; Saur et al 2006). For patients with large lesions that cover the language-relevant regions on the left, therapies that specifically engage homologue right-hemisphere regions may have the potential to facilitate the language recovery process beyond the limitations of natural recovery (Schlaug et al 2008; Schlaug et al 2009b; Vines et al 2009). One therapy that has made the claim of facilitating recovery from severe non-fluent aphasia as a result of large left hemisphere lesions is Melodic Intonation Therapy (MIT; (Albert et al 1973; Sparks et al 1974). MIT was developed in response to the observation that severely aphasic patients can often produce well articulated, linguistically accurate words while singing, but not during speech (Gerstman, 1964; Geschwind, 1971; Hebert et al 2003; Keith & Aronson, 1975; Kinsella et al 1988; Schlaug et al 2008). MIT uses intoned (sung) patterns to exaggerate the normal melodic content of speech by translating prosodic speech patterns into two pitches (high and low). The two unique elements which set MIT apart from other, non-intonation-based therapies are the melodic intonation (singing) with its inherent continuous voicing, and the rhythmic tapping of each syllable – using the patient's left hand – while phrases are intoned and repeated (for

more details on MIT see Norton et al 2009). The efficacy of MIT is still disputed and it is also not clear whether MIT – as suggested by the original developers (Albert et al 1973; Sparks et al 1974) – facilitates recovery through right hemisphere brain regions or regions on both sides of the brain and specifically left prefrontal regions. The latter was indicated by an imaging study by Belin and colleagues (1996) which had patients undergo a French version of Melodic Intonation Therapy and subsequently tested their intoned and non-intoned word reproduction using position emission tomography.

An alternative explanation has been that MIT may exert its effect by either unmasking existing music and language connections in both hemispheres, or by engaging preserved language-capable regions in either or both hemispheres. Since MIT incorporates both the melodic and rhythmic aspects of music (Albert et al 1973; Boucher 2001; Cohen 1993; Helm-Estabrooks 1989; Norton et al 2009; Sparks et al 1974; Sparks & Holland 1976), it may be unique in its potential for engaging not only the right, but both hemispheres. In the current study we aimed to investigate the behavioral and neural correlates of intensive MIT in an open label proof-of-concept trial in a group of 14 chronic patients with moderate to severe non-fluent aphasia and relatively unimpaired comprehension. Two pre-treatment assessments to determine the stability of baseline impairments were compared with each other and with multiple interim and post-treatment assessments to assess any improvement in speech output from a stable baseline and to relate this improvement to functional imaging changes of overt speaking tasks.

Methods

Participants

14 chronic stroke patients (13 males, 1 female, mean age 54.0, SD 14.2) with persistent moderate to severe non-fluent aphasia and relatively unimpaired comprehension were enrolled in our study which included 2 pre-treatment, one interim and 2 post-treatment assessments as well as a total of 3 functional imaging studies, two functional imaging studies pre-therapy and one study post-therapy. Patients were recruited through our Stroke Service and Neurorehabilitation Service as well as flyers posted in rehabilitation centers. The study was approved by the local institutional review board (IRB) and all subjects gave written informed consent.

To determine study eligibility, patients were interviewed and underwent subtests of the Boston Diagnostic Aphasia Examination (BDAE 2nd edition; Goodglass & Kaplan 1983) to classify their aphasic syndrome and to determine their baseline level of fluency and comprehension.

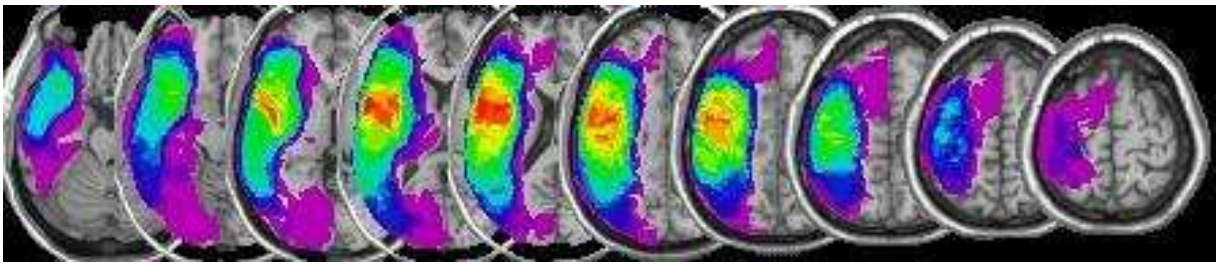

Figure 1: Collective Lesionmap for the 14 patients.

In order to be enrolled patients had to fulfill the following criteria: 1) age between 21 and 80 years, 2) at least 1 year from first and only ischemic, left-hemisphere stroke at therapy begin, 3) moderate to severely restricted verbal output including those patients whose output was confined to nonsense stereotypy (e.g., "bika bika"), and 4) moderately preserved auditory comprehension (e.g., understanding one-step commands and able to repeat at least 3 syllable words and phrases).

Patients	**Age** *yrs*	**T_{post}** *mo*	**Sex**	**HD**	**Side**	**Type**	**Size** *cc*	**AF-LL** *cc*
1	29	120	M	L/ambi	L	MCA	191.656	9.86
2	47	14	M	R	L	MCA	151.528	2.97
3	73	12	M	R	L	MCA	112.616	3.12
4	80	12	M	R	L	MCA	59.904	2.13
5	54	64	M	L	L	MCA	218.352	7.76
6	57	59	M	R	L	MCA	93.216	3.97
7	62	36	M	R	L	MCA	86.056	3.81
8	56	52	M	R	L	MCA	152.176	6.13
9	70	14	M	R	L	MCA	86.224	2.99
10	34	12	M	R	L	MCA	190.744	3.68
11	47	14	F	R	L	MCA	279.072	6.83
12	44	46	M	R	L	MCA	267.160	6.33
13	48	22	M	R	L	MCA	241.380	5.49
14	55	14	M	R	L	MCA	264.120	7.15
Mean	**54.0** ± 14.2	**35.1** ± 31.1					**171.0** ± 75.7	**5.2** ± 2.3

Table 1: Demographic and Clinical Data for the 14 patients. (Note: Age = age at treatment; T_{post} = Time post stroke; HD = handedness; AF-LL= AF-lesionload)

Exclusion criteria were: 1) cognitive deficits that impaired patients' ability to give informed consent or to competently participate in the study, (a score of less than the 50th percentile for their age on the Raven's Colored Progressive Matrices (RCPM; Raven, 1995) was used as a cut-off, 2) active medical or psychiatric conditions that would prevent participation in the

intense treatment study or follow-up assessments, 3) any MRI risk factors, 4) right-hemisphere ischemic stroke or crossed aphasia, 5) evidence of other neurological disease from clinical history, patient examination, or imaging studies, 6) more than 2 weeks of formal Melodic Intonation Therapy during the first year after their stroke and prior to inclusion into this study. None of the patients were on any psychoactive medications at the time of enrollment or during the study. Relevant clinical and demographic parameters of the patient group are given in Table 1.

Language Assessments and Therapy

After the evaluation of speech production we identified three measures of functional relevance: words per minute (rate of speech), percent correct information units (CIUs) of total words uttered (informativeness), and CIUs per minute (overall efficiency of speech). The latter were selected as our primary outcome measure. CIUs were determined on tests eliciting spontaneous speech during conversational interviews (Borovsky et al 2007) regarding biographical data, medical history, daily activities, descriptions of complex pictures (e.g., the Cookie Theft picture from the BDAE; Picnic picture from WAB and others), and descriptions of routine procedures (e.g., preparing a favorite sandwich, cooking a favorite dish, working on a hobby or doing a simple repair job). Videotapes of patient assessments were transcribed, timed, and scored by blinded coders with backgrounds in communication disorders and speech language pathology. The definition of a CIU was based on the scoring rules described by Nicholas and Brookshire (1993). In order to be counted as CIU, words had to be intelligible in context as well as accurate, relevant, and informative with respect to the stimulus; meaningless utterances, inappropriate exclamations, incorrect responses, and/or perseverations were excluded prior to scoring.

Our secondary outcome measures were the remaining two measures of fluency (1) total words per minute, and (2) percent correct information units (CIUs) of total words, and in addition, we obtained performance in (3) confrontational picture naming task using an untimed version of the Boston Naming Test (BNT) (Kaplan et al 2001). Patients were given a full point for items they could name unassisted, 0.5 points for items they could name with help of a semantic or phonemic cue, 0.25 points for items they could identify by choosing the correct written word from a set of four words presented in conjunction with the picture stimulus.

To ensure a stable baseline, patients were tested twice, at least 2-4 weeks apart. If there was more than a 10% difference in performance between those two test sessions, a third session was conducted. The two baseline performance values (pre1 and pre2) were determined by those two last sessions. The same tests were then administered after 40 (post40) and 75 treat-

ment sessions (post75) as well as 4 weeks after the end of the treatment (post75+4) in order to assess maintenance of any effect without any intervening therapy. All our patients underwent the 75 treatment sessions which have been the recommended level of treatment for MIT (Albert et al. 1973; Sparks et al. 1974; Helm-Estabrooks 1989 & 1991; Norton et al 2009). Treatment commenced after the last baseline assessment, administered by the same therapist for 1.5 hours a day, five days per week.

Experimental Stimuli and fMRI Paradigm

Based on the words patients were capable of saying and repeating during their initial assessment, a list of 12-16 bi-syllabic words/phrases to be used in the fMRI experimental task was recorded by a native speaker of English using Adobe Audition 1.5 software (Adobe, San Jose, CA). The same list of words/phrases used at baseline was repeated during follow-up imaging sessions. The functional MRI experiment consisted of five conditions: two experimental; spoken or sung bi-syllabic words/phrases; and three control; humming, phonation, and silence. In the experimental conditions, patients heard an investigator saying/singing two-syllable words or phrases (presented at the rate of 1 syllable/sec) which they were asked to repeat exactly as heard after an auditory cue. A pause was placed between the stimulus and cue to increase the delay between auditory perception and MR acquisition, thereby reducing the possibility that the subsequent activation pattern would be confounded by the stimulus. In the silence condition, patients had to wait for the auditory cue, then take a breath as if they planned to respond, similar to the experimental conditions. All patients were trained on the fMRI task prior to the baseline experiment, and a brief review of the task was conducted prior to each of the subsequent scans. Patients were trained to keep their eyes closed throughout the scanning session (for more details on the fMRI tasks see Ozdemir et al., 2006).

MR Data Acquisition

Functional magnetic resonance imaging (fMRI) was performed on a GE 3.0 Tesla whole-body MR scanner. A gradient-echo EPI-sequence with an effective repetition time (TR) of 15s, an echo time (TE) of 25ms, an acquisition time (TA) of 1.75s, and a matrix of 64x64 was used for functional imaging. Using a midsagittal scout image, a total of 28 axial slices with a voxel size of 3.75x3.75x5 were acquired over a period of 1.75 seconds after each trial. Initiation of the first image in the set of 28 slices was synchronized with the stimulus presentation using Presentation software version 7.2.6 (Neurobehavioral systems, Albany, CA). Stimuli were presented binaurally via scanner-compatible headphones. Although the TR was constant at 15s, the delay between subjects' responses and the onset of the MR acquisition was varied by moving the experimental trials within the 15s time frame. This 'jittering' provided sets of axi-

al images with delays of 3.5, 4.5, 5.5 and 6.5 seconds from the auditory cue for the first image in the stack of axial slices (for more details on this jittering approach see Gaab et al., 2003 and Ozdemir et al., 2006). By combining the data from all four jitter points, we were able to capture the peak hemodynamic response within the brain while allowing for timing differences between subjects and brain regions.

The fMRI experiment consisted of 8 runs, 20 trials per run (4 trials for each of the 5 conditions) plus 2 dummy scans at the beginning. The inter-stimulus interval was 15 seconds (TR=15) and thus, each run lasted 5.5 minutes. Our experimental set-up with recording subject's responses allowed us to verify that each of our subjects responded after each trial and that their rate of response was approximately one syllable per second.

fMRI Data Analysis

fMRI data were analyzed using the SPM5 software package (Institute of Neurology, London, UK) including realignment, spatial normalization, and smoothing using an isotropic Gaussian kernel of 8mm full-width at half-maximum. Condition and subject effects were estimated according to the general linear model (Friston, 2002). Each scan was scaled in proportion to its global intensity to remove the effect of global differences in scan intensity. Low-frequency drifts were removed using a temporal high-pass filter with a cutoff of 128 seconds (as suggested by the SPM software). A box-car function was applied to the fMRI time series with an epoch length of one. Because of the nature of the sparse temporal sampling design, we did not convolve our data with the hemodynamic response function (HRF), nor apply a low-pass filter (Gaab et al., 2003) or temporal derivatives. A Finite Impulse Response (FIR) was used as a basis function instead.

A design matrix was modeled by combining all individual imaging time points in order to look at the condition effects for each subject separately. Each condition was contrasted with the silence condition. For the purpose of this paper, we report only the Speaking vs Silence-control condition. Subsequently, we entered all patients' pre1 and post75 time points into a fixed effects group analysis using the group lesionmap as explicit mask, in order to assess the functional effects of MIT across all subjects. The contrasts speak > silence pre therapy, speak > silence post therapy (both FWE $p<0.05$ corrected) and the subtraction speak post > pre (FDR $p<0.05$) were created. In addition to the fixed effects model, we entered the contrasts of all timepoints (pre1, pre2, post40, post75) into a random effects full factorial design. For the full-factorial model we used a mask to reduce the search volume to a large right hemispheric perisylvian network. The mask image was generated by adding motor, temporal, parietal and frontal regions from the WFU PickAtlas Tool (version 1.04) and multiplying this binary mask

with a gray matter mask. The obtained mask was then inserted as an explicit mask into the full factorial model. We focused on the differences between the two baseline scans, as well as the effect of post75 versus the pre1 assessment (all contrasts at an uncorrected threshold $p<0.05$). Using MarsBaR (Brett et al., 2002), we extracted all activation clusters from both, fixed effect post75>pre1 contrast (FDR) as well as the random effects post75>pre1 contrast (uncorrected 0.05) and subsequently ran a ROI analysis by overlaying all ROIs onto each patients' pre1>silence and post75>silence contrast in order to obtain the mean intensity beta values. In SPSS, the absolute change score of these values were then correlated with the change scores of our primary outcome measure CIUs/min, as well as our secondary measures words/min, %CIUs and BNT.

Results

Effects of MIT on Behavioral Outcomes

Our primary outcome measure was correct information units per minute (CIUs/min) which was assessed at pre1+2, post40, post75, and at post75+4 timepoints. A repeated measures ANOVA revealed significant overall differences in CIUs/min across the 5 assessments (Greenhouse-Geisser corrected $F=16.952$, $p<0.001$). Post-hoc pairwise comparisons, showed no difference between the 2 pre-therapy assessments ($p=1.0$), but significant differences were found between the first baseline assessment and all other timepoints (post40, post75, post75+4wks; all $p>.015$). No significant differences were seen between post40 and post75 ($p<0.399$), post40 and post75+4 ($p<0.504$) and between post75 and post75+4 ($p=1.0$). Across the 14 patients, the mean percent increase in their CIUs/min was 323.69% (SE 124.29) after 40 sessions of MIT, 407.74% (SE 97.62) after 75 sessions, and 373.57% (SE 93.99) 4 weeks post-treatment.

The repeated measures ANOVA conducted with our secondary outcome measures revealed for %CIUs a significant overall difference across the 5 assessment time points ($F=13.70$, $p<0.001$). Post-hoc pairwise comparisons, showed no difference between the 2 pre-therapy assessments ($p=1.0$). The differences between baseline assessments and post40 were not significant ($p=0.072$; $p=0.142$), but a statistically significant difference was observed between baselines and post75 ($p<0.001$). The comparison from both baseline timepoints to post75+4 showed a significant difference ($p<0.01$). Again, no significant differences were found between post40 and either post75 or post75+4 ($p<0.950$; $p<0.650$) or post75 and post75+4 ($p=1.0$ respectively). Across the 14 patients, the mean percent increase in their %CIU score was 140.25% (SE 55.47) after 40 sessions of MIT, 190.35% (SE 61.75) after 75 sessions, and

193.22% (SE 61.75) 4 weeks post-treatment.

For words/min the overall ANOVA yielded a strong significant result (Greenhouse-Geisser corrected F=6.48, p<0.005), however the pairwise comparisons showed neither a significant difference between the two baselines (p=1.0), both baselines and post40 (p=1.0), pre1 and post75 (p=0.052), post40 and post75 (p=0.340), post40 and post75+4 (p=1.0) nor post75 and post75+4 (p=1.0). The only statistical significant differences were found between baseline2 and post75 (p=0.041), baseline2 and post75+4 (p=0.038) as well as pre1 and post75+4 (p=0.018). The mean percent increase for words/min after 40 sessions of MIT was 75.81% (SE 32.26), after 75 sessions 120.85% (SE 37.28) and after 75+4 sessions 100.92% (SE 30.22).

A repeated measures ANOVA using the BNT as factor likewise revealed significant overall differences across all 5 timepoints (p<0.001). Post-hoc pairwise comparisons showed no difference between the 2 pre-therapy assessments (p=1.0), but significant differences between pre1 and all other assessments (p<0.05) as well as pre2 and post75 (p=0.006) were observed. The difference between pre2 and post40 and pre2 and post75+4 only revealed a significant trend (p=0.089; p=0.077). No significant difference was found comparing post40 with post75 (p=0.637), post40 with post75+4 (p=1.0), as well aspost75 with post75+4 (p=1.0). The mean percent increase across all patients in the BNT scores was 81.25.77 (SE 34.68) after 40 sessions of MIT, 162.89 (SE 100.38) after 75 sessions and 180.1 (SE 101.72) 4 weeks after the treatment.

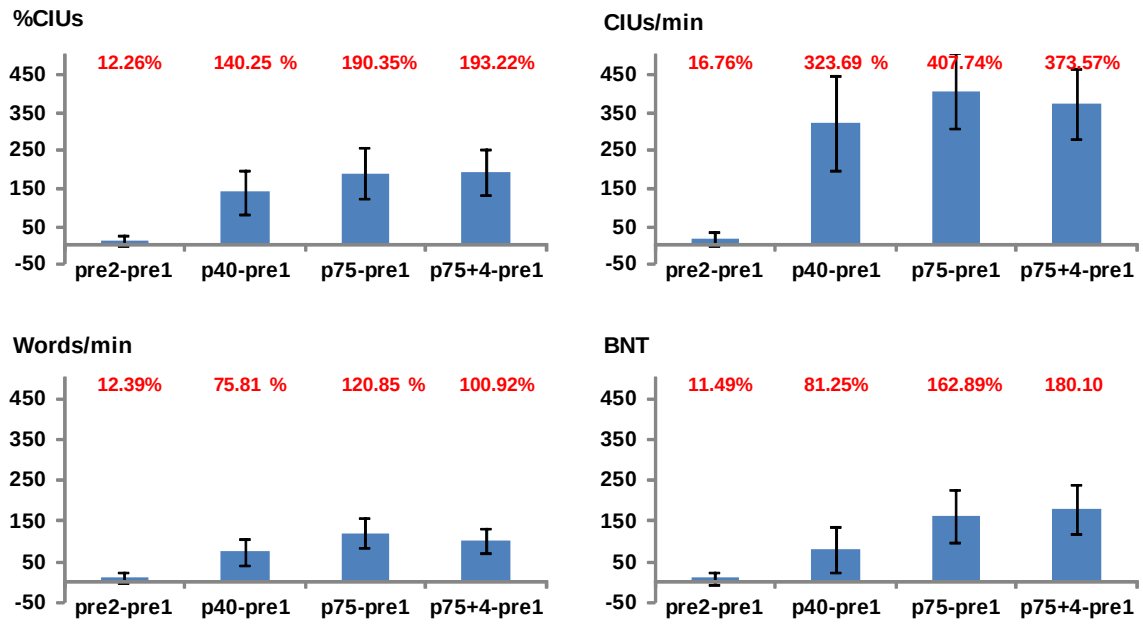

Figure 2: Mean percent improvement across the group for each of the 4 behavioral outcome measures comparing every timepoint with pre1.

Effects of MIT on the Brain Activation Pattern of Speaking

a) Activation pattern at baseline and after therapy

Significant activations (FWE $p<0.05$) in the speaking versus silence contrast prior to MIT treatment (pre1) were found in a right hemispheric network including pre- and post central gyrus, superior temporal gyrus (STG), superior temporal sulcus (STS), supplementary motor area (SMA) as well as the caudate nucleus. On the left hemisphere activated regions included the cerebellum, the SMA, the superior parietal lobule and the caudate nucleus.

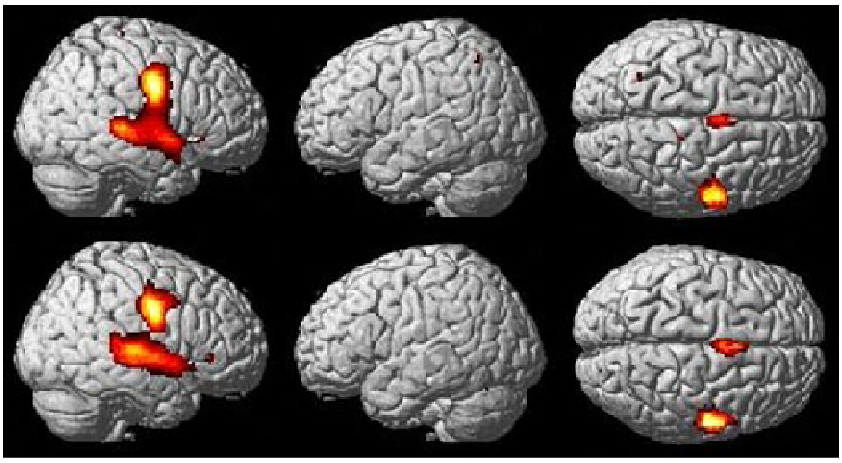

Figure 3: top row: pre therapy, FWE corrected ($p<0.05$); bottom row: post therapy, FWE corrected ($p<0.05$).

Following 75 sessions of MIT treatment speaking versus silence contrast (FWE $p<0.05$) showed an activation pattern including pre- and postcentral gyrus, superior temporal gyrus, inferior frontal gyrus (pars opercularis), SMA, cerebellum, cingulate cortex and caudate nucleus on the right hemisphere. Activated structures on the left hemisphere included SMA, thalamus and cerebellum.

b) Changes over time (fixed effects analysis)

The comparison of post versus pre treatment contrasts revealed a right perisylvian network including the superior temporal gyrus (STG), postcentral gyrus, the supramarginal gyrus (SMG) and the posterior part of the inferior frontal gyrus (pars opercularis) as well as the caudate nucleus. On the left the only activated region was the calcarine sulcus.

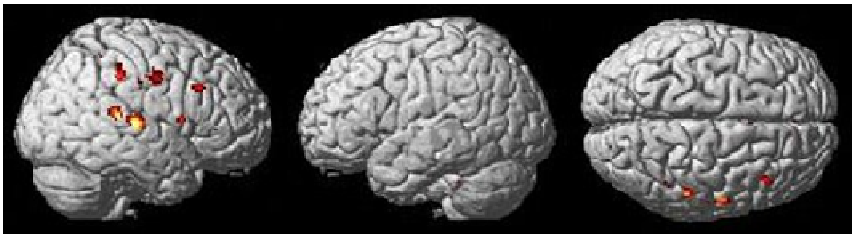

Figure 4: Post vs. Pre treatment comparison, FDR corrected ($p<0.05$).

c) Changes over time (random effects analysis)

The comparison of the two baseline scans reveals more prominent clusters in the inferior parietal lobe/parietal operculum, the precentral gyrus and the rolandic operculum. Smaller cluster were found in the middle temporal gyrus and the inferior frontal gyrus (pars orbitalis).

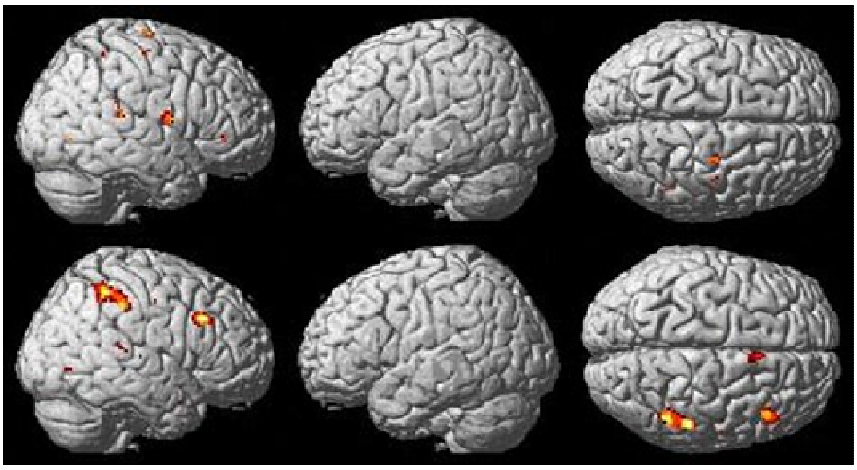

Figure 5: top row: pre2 vs. pre1, uncorrected ($p<0.05$); bottom row: post75 vs. pre1, uncorrected ($p<0.05$).

After 75 sessions of MIT (compared to pre1) we found a right hemispheric network consisting of two prominent clusters in the posterior IFG (pars triangularis), as well as the upper supramarginal gyrus (SMG). Smaller clusters were seen in the right SMA, the STG, the middle temporal gyrus, the temporal pole as well as the postcentral gyrus.

d) Associating behavioral changes with imaging changes

In order to assess whether activation changes in regions showing significant changes comparing pre with post-treatment imaging correlated with behavioral improvements, we correlated regional beta values as a measure of activation changes in the pars triangularis of the right posterior inferior frontal gyrus with behavioral improvement (post75 versus pre1).

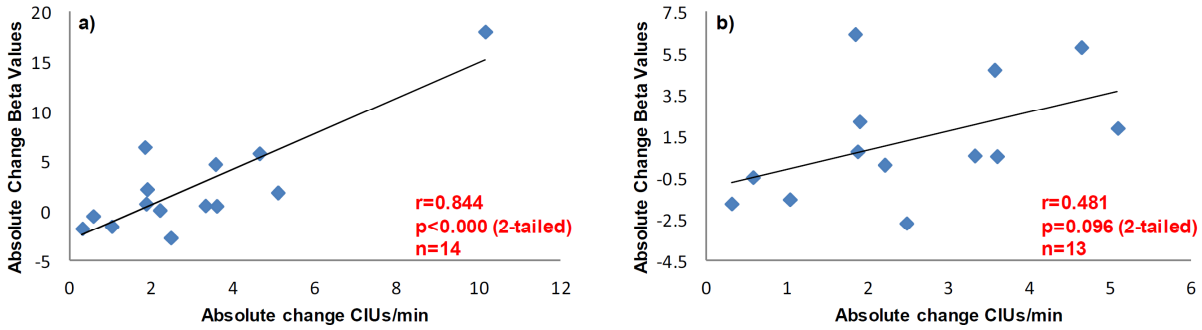

Figure 6: Correlations between the absolute change of the beta values derived from an ROI analysis and the behavioral outcome measure CIUs/min. a) shows the entire group of 14 patients; b) without the outlier which was suspected to drive the correlation.

We found a highly significant positive correlation between improvement in the patients' fluency, measured with CIUs/min and an increase in activation in the right inferior frontal gyrus ($r=0.844$, $p<0.001$). After excluding one outlier which we suspected to drive the correlation, there still remained a non-significant positive trend ($r=0.481$, $p=0.096$).

Discussion

In this study we examined the effects of long-term, intensive treatment with Melodic Intonation Therapy (MIT) on patients with large left-hemisphere lesions and chronic, nonfluent aphasia. In post- vs. pre-treatment behavioral comparisons, patients showed significant improvements in speech output, informativeness of content, and overall fluency after intensive MIT. In addition to the behavioral gains, significant functional imaging changes were observed in the right IFG, right SMG, pre-SMA, and right STG during overt, rate- and content-controlled speaking tasks. Further, changes in the right IFG were significantly correlated with improvement in speech output. Taken together, the post- vs. pre-treatment behavioral and imaging changes were significantly greater than the minor variations seen between pre-treatment (baseline) assessments, and perhaps more importantly, no significant difference was found in a comparison of the two post-treatment assessments, thus showing that patients were able to maintain their higher degree of fluency after the therapy had ended.

Our imaging data focuses on a classical language network of brain regions involved in (1) the mapping of sounds to articulatory actions (Lahav et al., 2007), and (2) the feedforward and feedback control of verbal output (Guenter et al., 2006). Although this language network has been shown to be bihemispheric in healthy brains, portions of it also appear to be capable of functioning independently when the primary network in the left hemisphere has sustained significant damage. In such cases, the secondary network in the undamaged right hemisphere must be both engaged and trained to perform the speech functions typically handled by the left hemisphere. The regions of this network communicate with one another via the arcuate fasciculus (AF), a white matter fiber tract that connects the frontal and temporal regions (Catani & Mesulam 2008; Glasser & Rilling 2008; Guenther et al 2006; Schlaug et al 2009a). While most DTI studies to date have located the AF and other language tracts (e.g., uncinate fasciculus and extreme capsule) in both hemispheres, they have also shown that the left-hemisphere AF is not only more elaborate and complex in its development and thus, may also reach more anteriorally into the frontal regions than its right-hemisphere counterpart (Vernooij et al 2007; Nucifora et al 2005; Matsumoto et al 2008; Glasser & Rilling 2008). It has been asserted that this might be an adaptation (plasticity) as the result of use-dependent

experience, since children don't have an AF that is as much lateralized as that of adults (Lebel & Beaulieu 2009). Nevertheless, if the left hemisphere network is destroyed, the brain seems to have the ability to specifically engage and potentially change the corresponding right hemisphere network as suggested by this study.

One of the more prominent regions where we observed a change after intensive therapy is the IFG which seems to be one of the main driving forces of this recovery process, since it is the only region which shows a positive correlation between signal changes over time and fluency measures. The IFG has been implicated in a number of functions (Liakakis et al., 2011; Costafreda et al., 2006; Vigneau et al., 2006; Nishitani et al., 2005), one of them being the mapping of sounds to speech motor actions and the sequencing of speech motor actions into behaviorally relevant units (Bangert & Altenmuller, 2003; Bangert et al., 2006).

The second region that stands out is the supramarginal gyrus. The strong activation of the right SMG over time might emphasize the role that the SMG could play in short-term storage and retrieval of phonological information/material (Jonides et al., 1998; Ravizza et al., 2004). Catani et al. (2005) described the inferior parietal region as a relay station between frontal and temporal cortical areas, and furthermore highlighted it as a separate primary language area with dense connections to classical language areas through the aforementioned AF (Catani et al., 2005). These interconnections of the inferior parietal cortex with regions such as the inferior frontal cortex and primary sensory areas suggest that it may be a crucial component in learning and adapting sensorimotor patterns for speech (Shum et al., 2011). More importantly, the IPL particularly the dorsal portion of the SMG is a vital part in the network for sensorimotor integration associated with speech motor learning to establish new speech motor patterns and subsequent sensorimotor plasticity (Shum et al., 2011; Rauschecker, 2010). This is in alignment with the results of this study which shows an increase in activation in the SMG after intensive speech motor learning in form of MIT. Taken this together with the IFG as well as the STG activation, our results confirm the notion of the inferior parietal region as a relay station involved in a sensory motor integration network served by the AF.

The observed activation in the frontomesial region encompasses the pre-SMA, the anterior – functionally and anatomically distinct – portion of the SMA which lies anterior to the coronal plane through the anterior commissure (AC) (Rizzolatti et al., 1996; Picard & Strick, 1996). While the SMA proper – the caudal part of the SMA – is considered to be related to motor execution, the pre-SMA seems to be more involved in the selection and preparation of movement (Picard & Strick, 1996). In their review, Cunnington et al. (2005) suggest that the pre-SMA plays a common role in encoding or representing actions prior to our own voluntary

self-initiated movements, during motor imagery, and from the observation of others' actions. The authors suggest that the pre-SMA generates and encodes motor representations which are then maintained in readiness for action (Cunnington et al., 2005; Cunninton et al., 1996). The pre-SMA is also involved in a wide variety of simple and complex overt language production tasks (Tremblay & Gracco, 2009). Some studies have shown that lesions to the SMA/pre-SMA often lead to a deficit in volitional spontaneous action and speech (e.g., Chainay et al., 2009; Mendez, 2004). Furthermore a case study by Deblieck et al. (2003) reported persistent difficulty with verbal fluency in a patient who underwent surgical removal of the pre-SMA, while naming, repetition and reading were preserved. Taken together these results show that the pre-SMA/SMA might be an important (usually preserved) region in the therapy and recovery process of non-fluent aphasia patients.

The region in the brain that showed the highest correlation between imaging changes and behavioral changes was the right posterior inferior frontal region. This is of particular importance, since the right pIFG, as the homolog region of left Broca's region might be directly involved in the mapping of sounds to articulatory actions which has been shown for motor actions (Lahav et al., 2007) as well as in the sequencing of phonemes into words and phrases (Gelfand & Bookheimer, 2003; Bohland & Guenther, 2006). MIT might train the association of sounds and articulatory actions with the goal of facilitating speech output. In a large meta-analysis using Activation Likelihood Estimation, Turkeltaub and colleagues (2011) found that activations in the right IFG were reliably observed in language production tasks in patients with aphasia and that the location of these activations corresponded with activation sites on the left hemisphere in healthy individuals (Turkeltaub et al 2011). Thus, it is not surprising that the right pIFG was found to be the only region showing a significant correlation between behavioral changes and imaging changes. It might not only be the driving force of the therapy induced brain changes, but furthermore of critical importance for the behavioral improvement. This finding seems to disagree with the result of an early MIT study conducted by Belin and colleagues (1996), who suggest that MIT-facilitated recovery could be associated with the reactivation of left-hemisphere regions, most notably the left prefrontal cortex, anterior to Broca's region. At first glance, the findings may appear inconsistent with the hypotheses put forth by the original developers of MIT and also with subsequent imaging studies (Albert et al 1973; Bonakdarpour et al 2000; Schlaug et al 2008; Schlaug et al 2009b; Schlaug et al 2010b; Sparks et al 1974). However, whilst their primary finding was an activation of left prefrontal regions when participants were asked to repeat intoned words, Belin and colleagues (1996) also reported blood flow changes in the right hemisphere (including the right temporal lobe

and the right central operculum) when comparing the repetition of spoken words with the hearing of those words. Thus, it appears that their results also point to the involvement of right hemisphere structures during language processing in patients with aphasia who had been treated with MIT.

The rationale for using an intonation based therapy for the recovery of aphasia is the dissociation between speaking and singing in aphasic patients. The traditional explanation for this dissociation is the presence of two routes of words articulation: One for spoken words through the brain's left hemisphere, and a separate route for sung words that uses either the right or both hemispheres. The small amount of empirical data available supports a bi-hemispheric role and potentially duplicate function for the execution and sensorimotor control of vocal production for both speaking and singing (Bohland & Guenther 2006; Brown et al 2004; Guenther et al 1998; Jeffries et al 2003; Ozdemir et al 2006). A tendency for greater left-lateralization for speaking under normal physiological conditions may have developed since constraints of transcallosal transfer time may have forced most operations to take part on one hemisphere (Ringo et al 1994). However, if both hemispheres have the potential for vocal production independently of each other assuming that posterior perisylvian comprehension regions on the left hemisphere are intact, then the question of why an intervention that uses singing, or a form of intoned speaking such as MIT, has the potential to facilitate syllable and word production still remains. In theory, there are four possible mechanisms by which the therapeutic effect of MIT could be achieved. Firstly the reduction of speed: sang words are articulated at a slower rate than spoken ones which might reduce the dependence on the left-hemisphere for vocal production. The rate of one syllable/s is the rate suggested by the developers of MIT (Helm-Estabrooks 1989; Koelsch et al 2005; Koelsch et al 2002; Patel 2003; Peretz & Coltheart 2003). Although we have made some adjustments to the original MIT protocol (Norton et al 2009), we did find the slow rate of vocalization particularly useful as a starting rate for our patients. In fact, many of our patients are so severely impaired at baseline that anything more than 1 syllable/s is too fast for them initially. Therapists are trained to adhere to the one syllable/s rate and the adherence to this rule is monitored by observing video recordings of the therapy sessions. When patients reach the "Advanced Level" of MIT, the rate is gradually increased to approximately 2 syllables/second as they are transitioned from singing back to speaking. A second component that could facilitate the MIT-induced effect is Syllable lengthening: It provides the opportunity to distinguish the individual phonemes that form words and phrases, while the continuous vocalization inherent in singing "strings" the sound together and thereby encourages fluency. This connected segmentation (i.e., overem-

phasizing the individual phonemes but still connecting them into meaningful words and phrases), coupled with the reduction of speed in singing may help nonfluent aphasic patients practice auditory-motor mapping under feedback control. This might lead to an increase in fluency, and may receive greater support from right-hemisphere structures. The third factor is Syllable "chunking": Prosodic features such as intonation, change in pitch, and syllabic stress may help patients group syllables into words and words into phrases, and this "chunking" may also enlist more right-hemisphere support. It has also been shown that tasks emphasizing prosodic information in perceptual as well as production tasks in normal healthy subjects lead to more right- than left-hemispheric activation (Meyer et al 2002; Ozdemir et al 2006; Zatorre & Belin 2001). Further, patients with right-hemisphere lesions have greater difficulty with global processing tasks (e.g., melody and contour processing) than those with left-hemisphere lesions (Peretz 1990; Schuppert et al 2000). Thus, it is possible that the melodic element of MIT engages the right hemisphere, particularly the right temporal lobe, more than therapies that do not make use of tonal information and melodic contour.

And last but not least, the role of the Left Hand Tapping (one tap/syllable, one syllable/second) cannot be underestimated, since it most likely engages a right-hemispheric, sensorimotor network which may, in turn, provide an impulse for verbal production in much the same way that a metronome has been shown to serve as a "pacemaker" in other situations in which rhythmic motor activities can prime and entrain a sensorimotor network (Thaut & Abiru 2010; Thaut et al 1999). In addition, there may be a set of shared neural correlates that control both hand movements and articulatory movements (Gentilucci et al 2000; Meister et al 2003; Tokimura et al 1996; Uozumi et al 2004), and furthermore, the sound produced by the tapping may encourage auditory-motor coupling or mapping of sounds to actions (Lahav et al 2007). Since concurrent speech and hand use occurs in daily life and gestures are frequently used during speech, hand movements, possibly in synchrony with articulatory movements, may have a facilitating effect on speech production, however, the precise role of this facilitation is unknown. We hypothesize that tapping the left hand may engage a right-hemispheric sensorimotor network that coordinates not only hand movements but orofacial and articulatory movements as well, and may facilitate speech production through rhythmic anticipation, rhythmic entrainment, or auditory-motor coupling (Lahav et al 2007; Schlaug et al 2010a; Thaut & Abiru 2010; Thaut et al 1999; Wan et al 2010).

In theory, reduction of speed, syllable lengthening, and syllable chunking can be applied to non-intonation based speech technique. However, these components are often not featured in the traditional speech therapy context.

Conclusions: The clinical observation that patients with nonfluent aphasia are better at singing lyrics than they are at speaking the same words inspired the development of Melodic Intonation Therapy (MIT). Despite several small case series, the efficacy of MIT has not been substantiated and its neural correlates remain largely unexplored. The current study contributes to the efficacy of MIT, although the ultimate proof will be a randomized clinical trial which is ongoing at this moment. The neural correlates of MIT have also not been examined in a large study using a pre-post design. The observed brain changes following treatment indicate that MIT's unique engagement of predominantly right-hemispheric brain regions (including the superior temporal region, the inferior parietal, the primary sensorimotor and premotor cortices as well as the inferior frontal gyrus) and the connections between these regions (mainly through the arcuate fasciculus), accounts for its facilitating effect.

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6.3 Study 3: Evidence for Plasticity in White-Matter Tracts of Patients with Chronic Broca's Aphasia Undergoing Intense Intonation-based Speech Therapy

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Abstract

Recovery from aphasia can be achieved through recruitment of either perilesional brain regions in the affected hemisphere or homologous language regions in the nonlesional hemisphere. For patients with large left-hemisphere lesions, recovery through the right hemisphere may be the only possible path. The right-hemisphere regions most likely to play a role in this recovery process are the superior temporal lobe (important for auditory feedback control), premotor regions/posterior inferior frontal gyrus (important for planning and sequencing of motor actions and for auditory-motor mapping), and the primary motor cortex (important for execution of vocal motor actions). These regions are connected reciprocally via a major fiber tract called the arcuate fasciculus (AF), however, this tract is not as well developed in the right hemisphere as it is in the dominant left. We tested whether an intonation-based speech therapy (i.e., melodic intonation therapy [MIT]), which is typically administered in an intense fashion with 75–80 daily therapy sessions, would lead to changes in white-matter tracts, particularly the AF. Using diffusion tensor imaging (DTI), we found a significant increase in the number of AF fibers and AF volume comparing post- with pretreatment assessments in six patients that could not be attributed to scan-to-scan variability. This suggests that intense, long-term MIT leads to remodeling of the right AF and may provide an explanation for the sustained therapy effects that were seen in these six patients.

Introduction

Aphasia is a condition characterized by either partial or total loss of the ability to communicate verbally. Aphasic disorders are classified according to fluency of verbal output as either fluent or nonfluent aphasia. Nonfluent aphasia most commonly results from a lesion in the left frontal lobe involving the left pos- terior inferior frontal region known as Broca's area (Kertesz et al. 1977) Patients who are nonfluent usually have the ability to comprehend the speech of others, but are unable to produce words themselves. Fluent aphasia generally results from a lesion involving the posterior superior temporal lobe known as Wernicke's area. While these patients' verbal output can be relatively fluent, they may have a prominent comprehension deficit and their jargon-like and/or nonsensical speech is often incomprehensible. The posterior superior temporal region (Wernicke's area) and the posterior inferior frontal region (Broca's area) as well as the adjacent premotor cortex are connected via a prominent fiber bundle called the arcuate fasciculus (AF) (Glasser and Rilling, 2008). A disruption of just this fiber bundle results in a characteristic aphasic disorder known as conduction aphasia. Patients with conduction aphasia are fluent and have relatively good comprehension, although their ability to repeat words and phrases is significantly impaired (Kertesz et al., 1977). If a stroke affects the AF fiber bundle and its anterior target regions, then the clinical presentation is usually that of a nonfluent or dysfluent Broca's aphasia with a greater or lesser degree of impairment to repetition, but relatively intact comprehension. Most patients with aphasia undergo speech therapy in the subacute to chronic phase, but the outcome in moderate to severely nonfluent patients with large left-hemisphere lesions is often dismal, even with intensive speech therapy. Although the efficacy of speech therapy in general has been shown in several meta-analyses, these analyses have also revealed that therapies might only lead to a measurable effect if the intervention is both intense and long-term (Robey, 1994). Functional imaging methods, such as positron emission tomography and functional magnetic resonance imaging (fMRI), have been used to reveal the functional neural correlates of language recovery, mostly using one assessment either at the presumed end of natural recovery or at the end of an experimental study. The general consensus across all of these studies is that there are two routes to recovery. In patients with small lesions, there tends to be more activation of left-hemisphere perilesional cortex and variable right-hemisphere activation either during the recovery process or after recovery. In patients with large left-hemisphere lesions involving most, if not all of the language-capable regions in the left fronto-temporal lobes, there tends to be more activation of homologous right-hemisphere language regions (Weiller et al., 1995; Heiss et al., 1999; Cappa and Vallar, 1992; Rosen et al., 2000; Winhuisen et al., 2005; Heiss and Thiel,

2006; Saur et al., 2006; Schlaug et al., 2008) Interestingly, relatively few studies have examined the neural correlates of an aphasia treatment by contrasting pre- and posttherapy assessments (Saur et al., 2006; Schlaug et al., 2008; Cornelissen et al., 2003; Musso et al., 1999; Small et al., 1998; Thompson and Shapiro, 2005).

Structural correlates of language recovery have not yet been examined. Voxel-based morphometry methods may be sensitive enough to detect changes in gray-matter densities or graymatter volume, but more meaningful methods might be those capable of detecting changes in connectivity between regions that must function in concert in order to restore any degree of language function after a stroke. In the present study, we aimed to use diffusion tensor imaging (DTI) to examine possible connectivity changes in chronic aphasic patients undergoing intensive therapy. DTI is a magnetic resonance imaging (MRI) technique that provides information about the diffusion of water molecules (Brownian motion) in the brain. The diffusivity of water molecules provides information about the brain's microstructure: in regions with high diffusion that has directionality, nerve fibers are likely to go in a similar direction. There has been increasing interest in the DTI technique not only because it allows us to study normal white-matter anatomy and structural connectivity (Basser et al., 1994; Mori and Zhan, 2006), but also because it allows us to study potential remodeling of white-matter tracts in stroke patients who are undergoing intense rehabilitation. The method allows filtering of fibers that pass through desired regions of interest (ROIs). The resulting isolated tracts are depicted in a probabilistic map reflecting the likelihood of a structural connection between selected regions of the brain (Jones, 2008).

The one intervention that specifically seeks to engage homologous right-hemisphere language regions, and appears effective at doing so when it is done intensively over a long period of time, is melodic intonation therapy (MIT) (Albert et al., 1973; Sparks, et al., 1974). This method was developed in response to the observation that severely aphasic patients can often produce well-articulated, linguistically accurate words while singing, but not during speech (Gerstman, 1971; Geschwind, 1971; Hebet et al., 2003; Keith and Aronson, 1975; Kinsella et al., 1988). MIT is a hierarchically structured treatment that uses intoned (sung) patterns to exaggerate the normal melodic content of speech by translating prosodic speech patterns (spoken phrases) into melodically intoned patterns using just two pitches (Schlaug et al., 2008) MIT contains two unique elements that set it apart from other, nonintonation-based therapies: (1) the melodic intonation (singing) with its inherent continuous voicing, and (2) the rhythmic tapping of each syllable (using the patient's left hand) while phrases are intoned and repeated. Another important characteristic of MIT is that, unlike many therapies adminis-

tered in the chronic phase that involve one to two short sessions per week, MIT engages patients in intensive treatment totaling 1.5 h/day, 5 days/week, until the patient has mastered all three levels of MIT, usually after 75–80 or more sessions. Considering that MIT is applied in a very intense fashion, we aimed to examine whether the intensity of this intonation-based speech therapy in chronic nonfluent aphasic patients with relatively large left-hemisphere lesions would not only lead to functional changes in the brain as reported previously (Schlaug et al., 2008), but would also change brain structure. It is possible that the sustained therapy effects may actually be due to structural changes in a language network, whether it be one that already exists or one that must be established during the course of treatment in order for the therapy to successfully restore some degree of fluency. The critical structure that facilitates both speech production and its feedforward and feedback control system is the AF. This structure connects the posterior part of the temporal lobe and inferior parietal region with the inferior frontal region of the brain and is considered to be part of a larger structure, the superior longitudinal fasciculus. In the dominant hemisphere, this pathway is thought to connect Wernicke's area with Broca's area and is usually more developed than its homolog structure in the nondominant right hemisphere. We sought to determine whether or not the AF in the undamaged right hemisphere would show structural changes as a result of intensive, long-term treatment with MIT.

Methods

Patients

We selected six right-handed patients from a larger group of patients who had participated either in our MIT pilot studies or in our ongoing randomized clinical trial examining the behavioral and neural correlates of two speech therapies in nonfluent aphasic patients. These six patients were selected because they had moderate to severe nonfluent aphasia with relatively preserved comprehension and were at least 1 year since their first (and only) left-hemisphere stroke. In addition, they had undergone high-resolution MRI studies that had included DTI acquisitions both before and after therapy. In addition, several of these patients had two separate DTI studies done before therapy, which allowed us to examine possible scan-to-scan variability in DTI-derived measures and relate that variability to therapy-induced changes in DTI-derived measures. Behavioral assessments, which were done several times before therapy, after 75 therapy sessions, and again 1 month later, included the number of correct information units (CIUs)/min produced during spontaneous speech, picture descriptions, and descriptions of common procedures. Secondary outcome measures included correctly named

items on standard picture-naming tests, as well as syllables per phrase (Schlaug et al., 2008).

Imaging Assessments

Structural MRI with DTI was performed using a 3-Tesla General Electric scanner. Anatomic images were acquired using a T1-weighted, three-dimensional, magnetization-prepared, rapid-acquisition, gradient-echo (MPRAGE) with a voxel resolution of 0.93 × 0.93 × 1.5 mm. DTI was performed using a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence (TE1 = 86.9 ms, TR = 10,000 ms, FOV = 240 mm, matrix size = 128 × 128 voxels, slice thickness = 5.0 mm, no skip, NEX = 1). Twenty-five noncollinear directions with a b-value of 1000 s/mm2 and one direction with a b-value of 0 s/mm2 were acquired. Fractional anisotropy (FA) values, a measure of the degree of directional preference of water diffusion, were calculated within each brain voxel.

Data Analysis

Tractography was applied to the DTI data to reconstruct white-matter tracts by successively following the path of preferred direction of water diffusion when FA is higher than a selected threshold (Basser et al., 2000; Mori et al., 1999; Jones and Horsfield, 1999). By means of MedINRIA software version 1.5.3 (http://www-sop. inria.fr/asclepios/software/MedINRIA) (Fillard et al., 2006), diffusion tensors were calculated from all voxels within the brain, and fiber tracts were calculated by connecting adjacent voxels with similar principal eigenvectors, using a threshold FA value of 0.2 and a smoothness factor (a parameter ranging from 0 to 1 corresponding to the straightness of each fiber) of 0.2 for continuous fiber reconstruction (Thomas et al., 2005). Only fibers with lengths >10 mm were included. These parameters are similar to those used by others who applied a fiber assignment by continuous tracking algorithm (Schaechter et al., 2008; Weinstein et al., 1999). ROIs were drawn in each brain on sagittal slices (with visual control of the region in the other two orthogonal planes) by a single coder, who was blind to the status of the participants. We identified the AF according to published DTI atlases (Lawes et al., 2008; Wakana et al., 2004). We drew ROIs in the white matter underlying the posterior middle temporal gyrus (pMTG), which contains the largest posterior branch of the AF, and the posterior inferior frontal gyrus (pIFG) to constrain fiber tracts. Fibers were reconstructed using voxels in the pMTG as seed regions and voxels in the pIFG ROIs as the target region.

In addition to the AF fiber tract, we also identified and traced the corticospinal tract (CST) in order to relate AF fibers at each timepoint to an internal control fiber bundle to minimize possible whole-brain differences in diffusivity from timepoint to timepoint. There was no reason to expect that the CST in the nonaffected hemisphere would change in this group of chronic

stroke patients (who did not undergo occupational therapy during the time that they were enrolled in our study). The CST was determined by drawing ROIs in the posterior limb of the internal capsule (PLIC), the brain stem at a pontine level, and the white matter underlying the precentral gyrus in each hemisphere on the color-coded FA images. The analysis was started by drawing an ROI in the PLIC, which is known to include the CST from anatomic (Kretschmann, 1988) and MRI studies (Holodny et al., 2005; Kim et al., 2008; Zarei et al., 2007). The next ROI was drawn at a pontine level using a slice on which the superior cerebellar peduncle was visible, corresponding to z = −26 of a spatially normalized brain in Talairach and Tournoux space (Talairach and Tournoux, 1988). We added a logical AND-function so that only fibers passing through both ROIs were considered for further analysis. The third ROI was drawn in the precentral gyrus, including its underlying white matter at a level that corresponded to z = 64 mm of a spatially normalized brain. A logical AND-function was also added for this ROI so that only fibers that started in the precentral gyrus and passed through the PLIC and the pons were designated as the CST. After applying tractography, the identified fiber bundles were compared for tract fiber number and volume.

Results

The AF was successfully identified in the right hemisphere of all six aphasic patients, but could not be identified to its full extent in the left hemisphere because each of the six patients' strokes had destroyed the majority of the tract. Therefore, our analysis is restricted to post- versus pretreatment comparisons of right- hemisphere tracts. All six patients showed a significant increase in the absolute number of fibers in the right AF comparing post- versus pretreatment DTI studies (paired t-test, P = 0.04). One patient (Fig. 1) showed not only an increase in the absolute fibers of the AF, but also an increase in the fiber length after therapy.

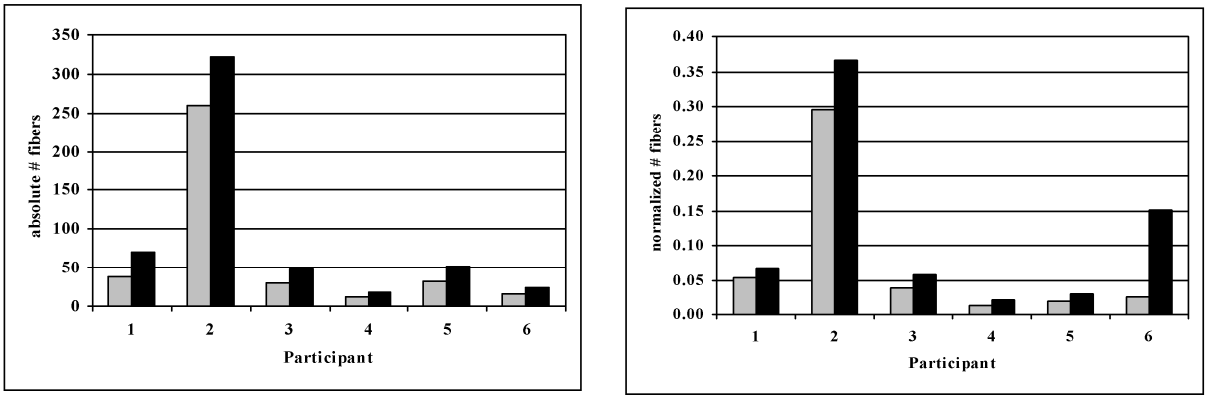

Figure 1: Absolute and relative fiber number of the right arcuate fasciculus (AF) before (gray bars) and after therapy (black bars) in all six participants.

The two pre-treatment DTI studies did not show any significant difference in the overall AF tract or in the total number of fibers. In order to normalize the pre- and the posttreatment measurement, we calculated a ratio between the fibers in the AF and the CST. Similar to the absolute differences seen in the post- verus preassessments, we also found a significant difference (paired t-test, P = 0.02) in the relative fiber numbers when the AF fibers were normalized with the fibers in the pyramidal tract (Fig. 2).

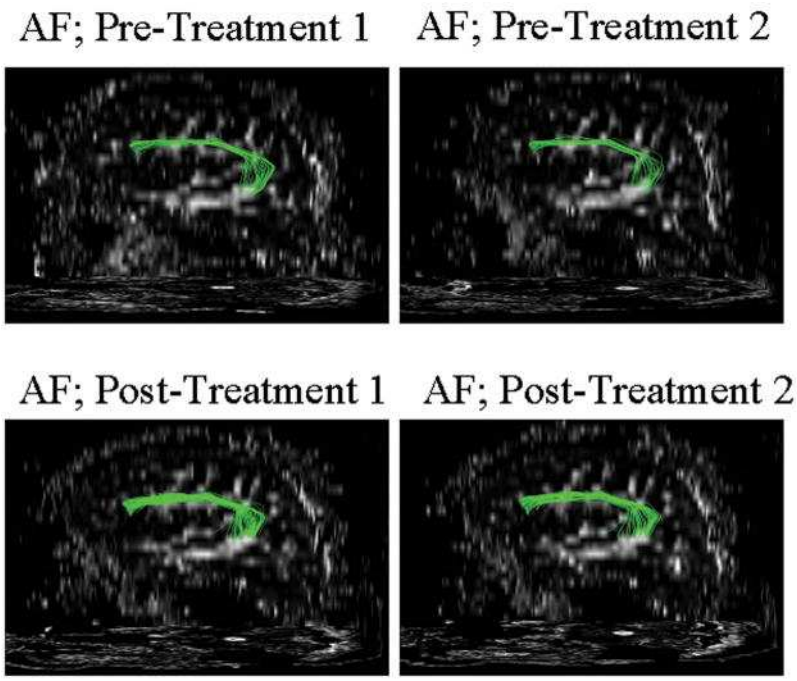

Figure 2: Right AF in one patient with two scans before therapy and two scans after 75 sessions of Melodic Intonation Therapy.
The scan-to-scan variability is minimal before therapy and a clear difference in the number of fibers and fiber volume can be seen in comparing the AF before and after therapy.

Because we had two pretreatment DTI studies in several patients we were able to assess scan-to-scan variations in the number of fibers present prior to therapy and compare this to the post- versus pretherapy differences. The scan-to-scan variability before therapy was very small and some patients even had identical fiber numbers. Thus, the post- versus pretreatment difference cannot be explained by scan-to-scan variability.

All six patients showed a significant improvement in speech outcome measures, such as the CIUs, while eliciting spontaneous speech through conversations with the patient and description of complex pictures as well as common procedures, the picture-naming test, and the number of syllables per phrase (Fig. 3).

By regressing change in CIU/min with change in AF fiber number, we found a strong trend for a correlation that did not reach significance, most likely because of the relatively small number of patients studied. Nevertheless, the observed trend let us conclude that the more a patient improved after therapy compared to before therapy, the more AF fibers were detected (r = 0.7; P = 0.1) (Fig. 4).

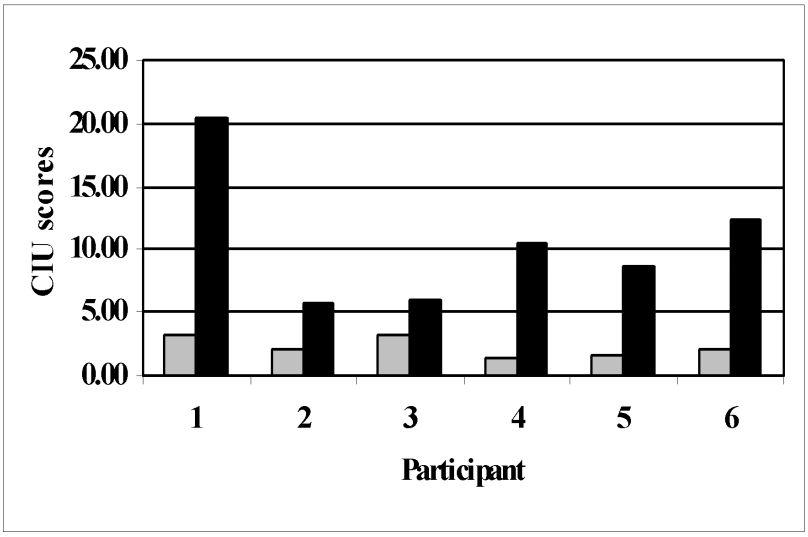

Figure 3: CIU/min before (gray bars) and after therapy (black bars) for all six participants.

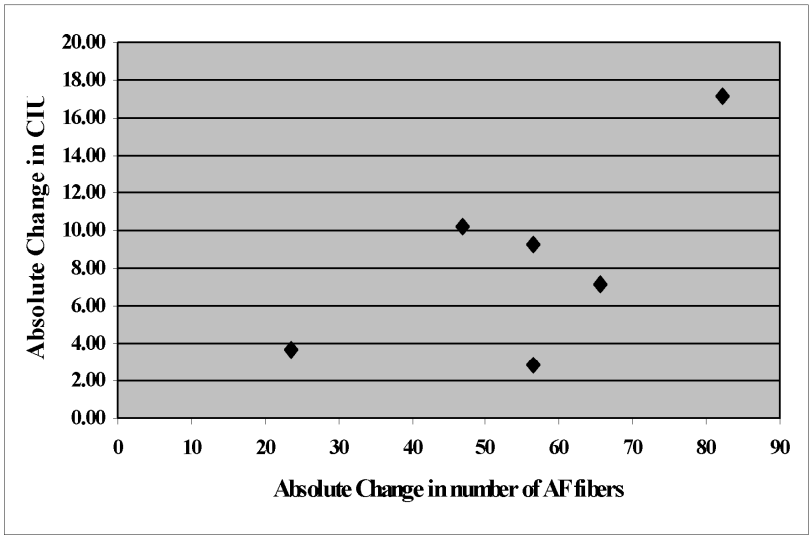

Figure 4: Correlation between absolute change in CIU/min and absolute change in number of AF fibers.

Discussion

The small amount of empirical data available supports a bi-hemispheric role in the execution and sensorimotor control of vocal prouction for both speaking and singing (Bohland and Guenther, 2006; Brown et al., 2004; Guenther et al., 1998; Jeffries et al., 2003; Ozdemir et al., 2003), with a tendency toward greater left-lateralization for speaking under normal physiological conditions (i.e., faster rates of production during speaking than singing). The asymmetry of the language fiber tracts in fiber number/volume and fiber extent, among them the AF, might be a structural correlate of the left-hemisphere advantage for language functions, although the right hemisphere also plays a role in expressive language function.

The two unique elements of MIT that, most likely, make the strongest contribution to the therapy's beneficial effects are the melodic intonation (singing) with its inherent sustained

vocalization, and tapping with the left hand. How might melodic intonation influence recovery? Functional imaging tasks targeting the perception of musical components that require a more global than local processing strategy (e.g., melodic contour, musical phrasing, and/or meter) tend to elicit greater activity in right-hemispheric brain regions than in left-hemispheric regions. It has been shown that tasks that emphasize spectral information over temporal information have shown more right- than left-hemispheric activation (Zatorre and Belin, 2001).

Similarly, patients with right-hemisphere lesions have greater difficulty with global processing (e.g., melody and contour processing) than those with left-hemisphere lesions (Peretz, 1990; Schuppert et al., 2000). Thus, it is possible that the melodic element of MIT engages the right hemisphere, particularly the right temporal lobe, more than therapies that do not make use of pitch or melody. Furthermore, using melody and emphasizing prosodic features will lead to a general reduction in the vocalization rate as syllables are lengthened and "chunked" into larger structures.

The effects of tapping the left hand should be considered in the same context. Once the right temporal lobe is specifically engaged by the melodic intonation and melodic contour, it is conceivable that the role of the left hand-tapping could be the activation and priming of a right-hemispheric sensorimotor network for articulation. Since concurrent speech and hand use occurs in daily life, and gestures are frequently used during speech, hand movements, possibly in synchrony with articulatory movements, may have a facilitating effect on speech production, but the precise role of this facilitation is unknown. We hypothesize that tapping the left hand may engage a right-hemispheric sensorimotor network that coordinates not only hand movements but orofacial and articulatory movements as well. There is some evidence in the literature that such superordinate centers exist in the premotor cortex and share neural substrates for hand and orofacial movements (Meister et al., 2003; Tokimura et al., 1996; Uozumi et al., 2004). Furthermore, behavioral (Gentilucci et al., 2000), neurophysiological (Meister et al., 2003; Tokimura et al., 1996) and fMRI studies (Aziz-Zadeh et al., 2006; Koelsch et al., 2005; Lahav et al., 2007) have shown that motor and linguistic cortical representations of objects are closely linked, and that the premotor cortex may belong to an integrative network coordinating motor and lin- guistic expression. An additional or alternative explanation is that the left hand tapping may serve the same function as a pacemaker or metronome has in rehabilitation of other motor activities, and in so doing, may facilitate speech production through rhythmic anticipation, rhythmic entrainment, or auditory-motor coupling (Lahav et al., 2007; Bangert and Altenmuller, 2003; Bangert et al., 2006).

The structural changes that we have detected in the AF must be seen in the context of what MIT actually does and the potential benefit that a patient may derive from the therapy. It is very clear that for the therapy to work well, the temporal lobe must strengthen its connections with the frontal lobe in order to provide fast feedback mechanisms for vocal articulation and for auditory-motor coupling (Lahav et al., 2007; Bangert and Altenmuller, 2003; Bangert et al., 2006) to take place in the right hemisphere. Mapping sounds to vocal motor actions is more of a left-hemisphere function, but that function is typically destroyed as part of the stroke that causes Broca's aphasia. Furthermore, the inferior frontal lobe needs to connect quickly with the premotor and motor regions in order to plan, prepare, and execute vocal actions. This feedforward system may be under corrective and/or adaptive control of the sensory feedback system in order to improve the auditory-motor mapping (Lahav et al., 2007; Bangert and Altenmuller, 2003; Bangert et al., 2006).

In this context, it would make sense that the tract that provides the connections between these major regions undergoes remodeling as part of the long-term therapy, in particular, if the therapy specifically engages the brain components that are part of this tract. Moreover, since the right AF is known to have slightly less volume and appears to be slightly shorter than it is on the left, it is also not surprising that the major change that seems to be occurring is in fiber number/volume, and possibly fiber length as we have seen in some of our patients. The components that underlie this structural change are not clear. Because our analysis suggests that there are more fibers, and we know that there is also more volume in this tract, it is possible that the myelinization of axons increases and that there is either additional axon growth or axon collaterals are being formed (Dancause et al., 2005). Furthermore, it is also possible that there are other physical changes to membranes that make fibers more traceable. Experimental studies in monkeys have shown that remodeling of fiber tracts, such as the formation of axon collateral, can happen after a focal stroke (Dancause et al., 2005). The establishment of axon collaterals in the affected hemisphere may actually change the cytoarchitecture in these regions, which, in turn, has direct effects on the diffusion of water molecules: the lower the alignment in the architecture, the lower the directionality in diffusion (and vice versa), consequently affecting fiber reconstruction.

It is clear that this change is not due to normal fluctuations in the measured parameters, since the variability between two DTI scans and their derived measures prior to therapy was very small, and the magnitude of change seen in the post- versus pretherapy comparisons was way beyond the level of scan-to-scan variability. It is possible that the remodeling of the AF might be triggered by the need for stronger, more effective connections between speech-relevant

brain regions in the right hemisphere. This remodeling could involve changes not only in myelination, but also in the axons themselves, possibly through the formation of axon collaterals, which could account for the increased number of fibers detected after therapy.

Acknowledgments

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6.4 Study 4: Impairment of Speech Production Predicted by Lesion Load of the Left Arcuate Fasciculus

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Abstract

Background and Purpose – Previous studies have suggested that patients' potential for poststroke language recovery is related to lesion size; however, lesion location may also be of importance, particularly when fiber tracts that are critical to the sensorimotor mapping of sounds for articulation (e.g., the arcuate fasciculus) have been damaged. In this study, we tested the hypothesis that lesion loads of the arcuate fasciculus (i.e., volume of arcuate fasciculus that is affected by a patient's lesion) and of 2 other tracts involved in language processing (the extreme capsule and the uncinate fasciculus) are inversely related to the severity of speech production impairments in patients with stroke with aphasia. ***Methods –*** Thirty patients with chronic stroke with residual impairments in speech production underwent high-resolution anatomic MRI and a battery of cognitive and language tests. Impairment was assessed using 3 functional measures of spontaneous speech (e.g., rate, informativeness, and overall efficiency) as well as naming ability. To quantitatively analyze the relationship between impairment scores and lesion load along the 3 fiber tracts, we calculated tract-lesion overlap volumes for each patient using probabilistic maps of the tracts derived from diffusion tensor images of 10 age-matched healthy subjects. ***Results –*** Regression analyses showed that arcuate fasciculus lesion load, but not extreme capsule or uncinate fasciculus lesion load or overall lesion size, significantly predicted rate, informativeness, and overall efficiency of speech as well as naming ability. ***Conclusions –*** A new variable, arcuate fasciculus lesion load, complements established voxel-based lesion mapping techniques and, in the future, may potentially be used to estimate impairment and recovery potential after stroke and refine inclusion criteria for experimental rehabilitation programs.

Introduction

Aphasia is a devastating complication of stroke that is characterized by an impairment in or loss of verbal communication ability. Although researchers have long attempted to identify the major predictors of recovery from this condition (Lazar and Antoniello, 2008), it remains difficult for clinicians to make accurate prognoses regarding speech and language deficits after stroke. In particular, the extent to which lesion size affects speech production remains unclear. Although some researchers (Kertesz et al., 1979; Pedersen et al., 1995) have reported lesion size to be a significant determinant of fluency after stroke, others have found no significant differences in lesion size between patients who recover fully and those who do not (Laska et al., 2001). Indeed, one recent study found no significant correlations between lesion size and severity of initial impairment or performance at 90 days. Furthermore, a regression model combining age, lesion size, and severity of initial impairment, although statistically significant, predicted <30% of the variance in speech outcome at 90 days (Lazar et al., 2008).

In their efforts to delineate the relationship between lesion size/location and degree of impairment, several recent studies have used voxel-based lesion–symptom mapping techniques to investigate the anatomic correlates of aphasia (Baldo et al., 2006; Bates et al., 2003; Borovsky et al., 2007; Piras and Marangolo, 2007; Schwartz et al., 2009). Some of these studies have suggested that the degree of white matter involvement plays a role in language deficits and recovery; however, the extent to which aphasia severity and recovery potential are affected by specific white matter damage – for example, the involvement of language-related fiber tracts – has not been assessed.

In this study, we examined 3 major language tracts previously identified by researchers: the arcuate fasciculus (AF), uncinate fasciculus (UF), and extreme capsule (EmC). The AF connects the superior and middle temporal gyri with the posterior inferior frontal lobe. Recent studies have suggested that the AF may be primarily involved in the mapping of sounds to articulation (Leclercq et al., 2010; Saur et al., 2008). In contrast, the UF and the EmC, which connect the temporal lobe to more anterior portions of the inferior frontal gyrus, are thought to be more involved in the mapping of sounds to meaning (Leclercq et al., 2010; Saur et al., 2008; Friederici, 2009). Thus, the aim of our study was to quantitatively examine the relationship between lesion size and location – as measured by extent of damage to these 3 language tracts – and impairment of fluent speech production. Speech fluency – a multidimensional parameter of speech production that encompasses various elements such as speech rate, phrase length, pauses, articulatory struggle and accuracy, prosody, syntactic structure, and so on – is notoriously difficult to measure and lacks a widely accepted standard measure (Hillis,

2010; Wilson et al., 2010). In the absence of such an assessment tool, we chose to evaluate fluency using 3 functional measures of conversational speech; this is in contrast to using clinical measures of speech production, which do not necessarily capture all aspects of speech and language that may be of importance to the patient or for recovery (Hillis, 2010).

Accordingly, we overlaid lesion maps of 30 patients with chronic stroke with probabilistic maps of the AF, UF, and EmC derived from diffusion tensor images of healthy, agematched subjects. Lesion loads (i.e., volume of tract affected by a patient's lesion) of these tracts were then calculated and related to 3 functional measures of speech production: words per minute (WPM), number of correct information units (CIUs) per total words uttered (%CIUs), and CIUs per minute (Nicholas and Brookshire, 1993). WPM reflects the rate of speech but includes uninformative "filler" words, circumlocutions, and incorrect words. A high WPM score therefore requires relatively intact articulatory abilities but does not necessarily require accurate retrieval of phonological word forms. Percent CIUs measures the informativeness of speech. This measure relies on retrieval of correct phonological word forms; semantic-tophonological connections must be relatively intact in order for %CIUs to be high. CIUs/min measures the efficiency of speech; a high score on this measure requires both adequate articulatory abilities and good retrieval of phonological word forms. In keeping with our interpretation of these 3 fluency measures, we hypothesized that lesion load would be a better predictor of impairment than lesion size alone and, furthermore, that AF lesion load would predict WPM, whereas UF and EmC lesion load would predict %CIUs.

Methods

Subjects

The study group consisted of 30 right-handed patients, all of whom had left-hemispheric strokes in the middle cerebral artery territory and were at least 11 months post stroke at the time of testing (6 females and 24 males; mean age 58.5 years [SD 10.0]; mean time poststroke 35.0 months [SD 28.7]). Although all patients had been diagnosed with severe nonfluent aphasia in the acute/subacute phase (based on assessments conducted during the initial hospitalization period), they had recovered to varying degrees at the time of study enrollment (see Supplemental Table I for details on patients; http://stroke.ahajournals.org). Exclusion criteria included bihemispheric or brain stem infarcts, primary intracerebral hemorrhages, previous or subsequent strokes, concomitant neurological diseases/disorders, and other aphasic syndromes such as pure anomia and those characterized by severe comprehension deficits (less than the 45th percentile on the combined Auditory Comprehension subtest scores on the Boston Diag-

nostic Aphasia Evaluation [BDAE] (Goodglass and Kaplan, 1983)) or cognitive impairments (less than the 50th percentile on the Raven's Colored Progressive Matrices (Raven, 1995)). Mean, SD, and range data both for patient test scores and assessment norms are shown in the Table below.

	RCPM	WPM	%CIUs	CIUs/min	BNT	BDAE_R
Patient group						
Mean	20.0	21.0	31.0	8.6	33.2	4.9
SD	3.4	15	24.3	11.9	17.4	3.3
Range	13–24	2.3–59.4	3.3–87.5	0.3–42.8	47–60	0–10
Normative values						
Mean	20.3	167.7	86.7	145.0	55.6	9.9
SD	3.3	22.0	6.0	21.0	3.0	0.3
Range	8–24	110–200	73–93	96–174	47–60	9–10

Table: Patient Data and Normative Values.

RCPM indicates Raven's Colored Progressive Matrices; WPM, words per min; CIUs, correct information units; BNT, Boston Naming Test; BDAE, Boston Diagnostic Aphasia Evaluation; SD, standard deviation.

Normative values are taken from Nicholas and Brookshire (1995) for CIUs, from the Boston Diagnostic Aphasia Examination and Boston Naming Test manual for Boston Diagnostic Aphasia Examination and Boston Naming Test scores; Smits et al. (1997) was used for the normative values for the Raven's Colored Progressive Matrices. In addition to the 30 patient participants, enrolled 10 healthy, right-handed, age-matched control subjects (3 women and 7 men; mean age 57.2 years [SD 15.7]). This study was approved by the local Institutional Review Board, and all participants gave written informed consent.

Behavioral Assessments

Spontaneous speech was elicited using conversational interviews (Borovsky et al., 2007) regarding biographical data, medical history, daily activities, descriptions of complex pictures (e.g., the Cookie Theft picture from the Boston Diagnostic Aphasia Examination), and descriptions of simple routine procedures (e.g., "Explain how you would make a peanut butter sandwich, cook a favorite dish, work on a hobby, do a simple repair"). Videotapes of patient assessments were transcribed, timed, and scored by blinded coders with backgrounds in communication disorders and speech language pathology.

Because there is no standard definition for fluency (Hillis, 2010; Wilson et al., 2010; Nicholas and Brookshire, 1993) and, as a result, no widely accepted means of assessing spontaneous speech, we chose to evaluate speech production by using 3 measures of functional relevance: WPM (rate of speech), percent CIUs of total words uttered (informativeness), and CIUs per minute (overall efficiency of speech). To be counted as CIUs, words had to be intelligible in context as well as accurate, relevant, and informative with respect to the stimulus; meaning-

less utterances, exclamations, inappropriate information, and perseverations were counted as words but not as CIUs (Nicholas and Brookshire, 1993). Intraobserver reliability as well as interobserver (2 coders) reliability for these 3 items was >0.9.

In addition to assessing spontaneous speech, we also evaluated each patient's naming ability using an untimed version of the Boston Naming Test (Kaplan et al., 2001). Patients were given a full point (1.0) for items they could name unassisted, 0.5 points for items named with help of a semantic or phonemic cue, and 0.25 points for items they could identify by choosing the correct written word (from a set of 4 words presented in conjunction with the picture stimulus).

MRI and Diffusion Tensor Imaging Acquisition

All patients and age-matched control subjects were scanned using a 3-Tesla General Electric scanner with a standard radiofrequency head coil. T1-weighted images (voxel resolution of 0.93x0.93x1.5 mm^3) were acquired and spatially normalized into images of isotropic voxel size (2x2x2 mm^3) using SPM5 (Wellcome Department of Neurology, London, UK) implemented in Matlab (The Mathworks Inc, Natick, MA). For patients with extensive lesions, masks were drawn in MRIcro (Rorden and Brett, 2000) to exclude the lesion from the cost function calculation of the spatial normalization process (Brett et al., 2001).

The control subjects underwent diffusion tensor imaging using a single-shot, spin-echo echoplanar imaging sequence with the following parameters: TR=10 seconds; TE=86.9 ms; resolution 2.6x2.6x2.6 mm^3; 30 noncollinear diffusion directions with a b-value of 1000 s/mm^2; and 6 acquisitions with a value of 0 s/mm^2. A total of 56 slices covered the entire brain, including the brain stem. Postprocessing of diffusion tensor imaging images and fiber-tracking were done as detailed in Zhu et al. (2010).

For the AF, a curved fiber bundle that connects the posterior portion of the temporoparietal junction with the frontal cortex (Catani et al., 2005) we drew 1 region of interest on the Fractional Anisotropy (FA) map in the white matter underlying the posterior middle and superior temporal gyri at approximately x=−50 mm (MNI space); a second region of interest was drawn on the same sagittal slice in the white matter underlying the pars opercularis of the posterior inferior frontal gyrus.

The UF is a hook-shaped fiber bundle that links the anterior portion of the temporal lobe with the orbital and inferior frontal gyri (Catani et al., 2008; Jellison et al., 2004). To reconstruct this tract, we drew coronal regions of interest in the anterior region of the corona radiata (y=37), the anterior part of the temporal lobe where the UF adjoins the inferior fronto-occipito fasciculus (Jellison et al., 2004; Kier et al., 2004), and in the white matter underlying the infe-

rior and middle temporal gyri (y=49).

The EmC is a fiber bundle that links the temporal and inferior frontal gyrus/inferior prefrontal regions (Saur et al., 2008; Makris and Pandya, 2009). To reconstruct the EmC, a region of interest was first drawn on a sagittal slice (x=−37) in the white matter underlying the pars orbitalis and triangularis in the inferior frontal gyrus; a second region of interest was drawn on the same slice in the midportion of the white matter underlying the superior temporal gyrus.

Lesion Mapping

We used MRIcro to define each patient's chronic lesion in the spatially normalized T1-weighted images while referring to the coregistered fluid-attenuated inversion recovery images for additional guidance. In some cases, we found marked ventricular dilatation due to extensive ischemic lesions and subsequent hemispheric atrophy. However, no part of the dilated ventricle was included in the lesion area. Lesions were drawn by a single rater who was blind to the patients' fluency/behavioral scores. A second rater, also naive to the patients' speech impairment scores, drew lesions in a subset of 10 patients to calculate an interobserver reliability, which was 0.93 for lesion volume.

Lesion Load Calculation

The reconstructed fiber tracts of the control subjects were transformed into binary images and then spatially normalized using SPM5. Overlaps between lesions and fiber tracts were calculated using the previously described raw lesion load method (Zhu et al., 2010). In brief, the binary fiber tracts of the 10 healthy control subjects were summed to generate a fiber map using Matlab (Figure 1). Voxel intensities ranged from I=0 (i.e., voxel is not part of the tract in any of the subjects) to I=10 (i.e., voxel is part of the tract in all 10 subjects); thus, the probability that a particular voxel would be part of the tract was calculated as one tenth of the voxel's intensity. For each lesion, a raw lesion-tract overlap volume (V_{raw}) was calculated by overlaying the lesion map onto the probabilistic fiber tract and summing the intensities of all intersecting voxels. This calculation is denoted by the equation

$$V_{\text{raw}} = \sum_{n=1}^{n_{\max}} \left[\frac{1}{10} \cdot I(n) \cdot (\text{voxel volume}) \right]$$

where $n_{\max}$ is the total number of intersecting voxels between the lesion map and fiber map and $I(n)$ is the intensity of the n^{th} voxel (as represented in the fiber map).

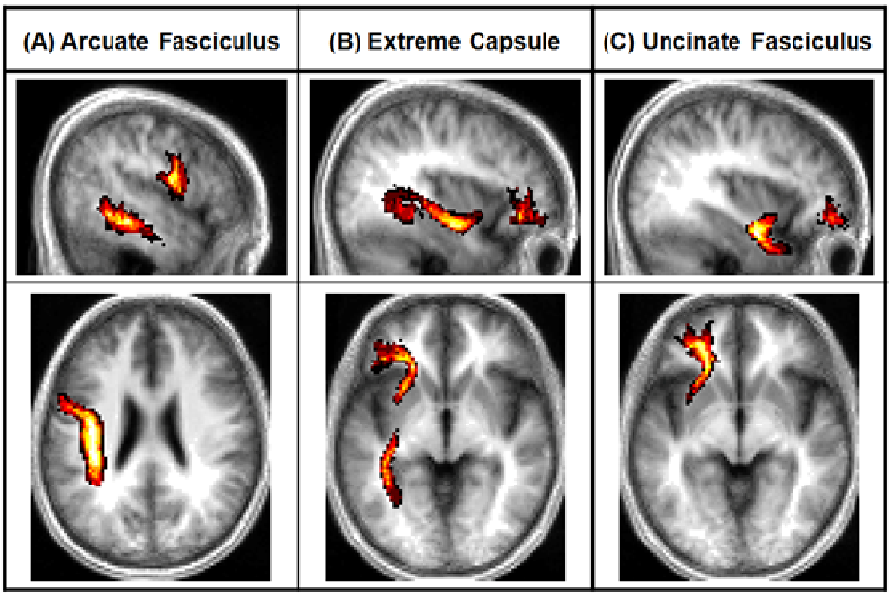

Figure 1: Lesion maps and probabilistic fiber tracts. Shown here are probabilistic maps of the (A) AF, (B) EmC, and (C) UF. The sagittal slices shown correspond to x=−50, −36, and −36 in Talairach space; the axial slices shown correspond to z=−26, −4, and −6.

Results

Rate of Speech

A regression analysis was first conducted using lesion size and lesion loads of all 3 tracts (i.e., AF, EmC, and UF) as predictors of words/min (adjusted R^2=0.301, P=0.011). AF lesion load proved to be the best variable (partial R^2=0.175, P=0.030; Figure 2A), whereas EmC lesion load (partial R^2=0.087, P=0.135), UF lesion load (partial R^2=0.098, P=0.112), and lesion size (partial R^2=0.002, P=0.829) were shown to be nonsignificant predictors.

Informativeness of Speech

A second regression analysis was conducted using the same 4 variables to predict %CIUs (adjusted R^2=0.496, P=0.001). Again, AF lesion load was shown to be a significant predictor (partial R^2=0.336, P=0.002; Figure 2B), whereas EmC lesion load (partial R^2=0.052, P=0.520), UF lesion load (partial R^2=0.058, P=0.227), and lesion size (partial R^2=0.002, P=0.844) were nonsignificant

Overall Efficiency of Speech

A third regression analysis was conducted using lesion size as well as AF, EmC, and UF lesion loads as predictors of CIUs/min (adjusted R^2=0.610, P=0.001). Once again, AF lesion load proved to be a significant predictor (partial R^2=0.450, P=0.001; Figure 2C), whereas EmC lesion load (partial R^2=0.086, P=0.138), UF lesion load (partial R^2=0.106, P=0.100), and lesion size (partial R^2=0.034, P=0.358) remained nonsignificant.

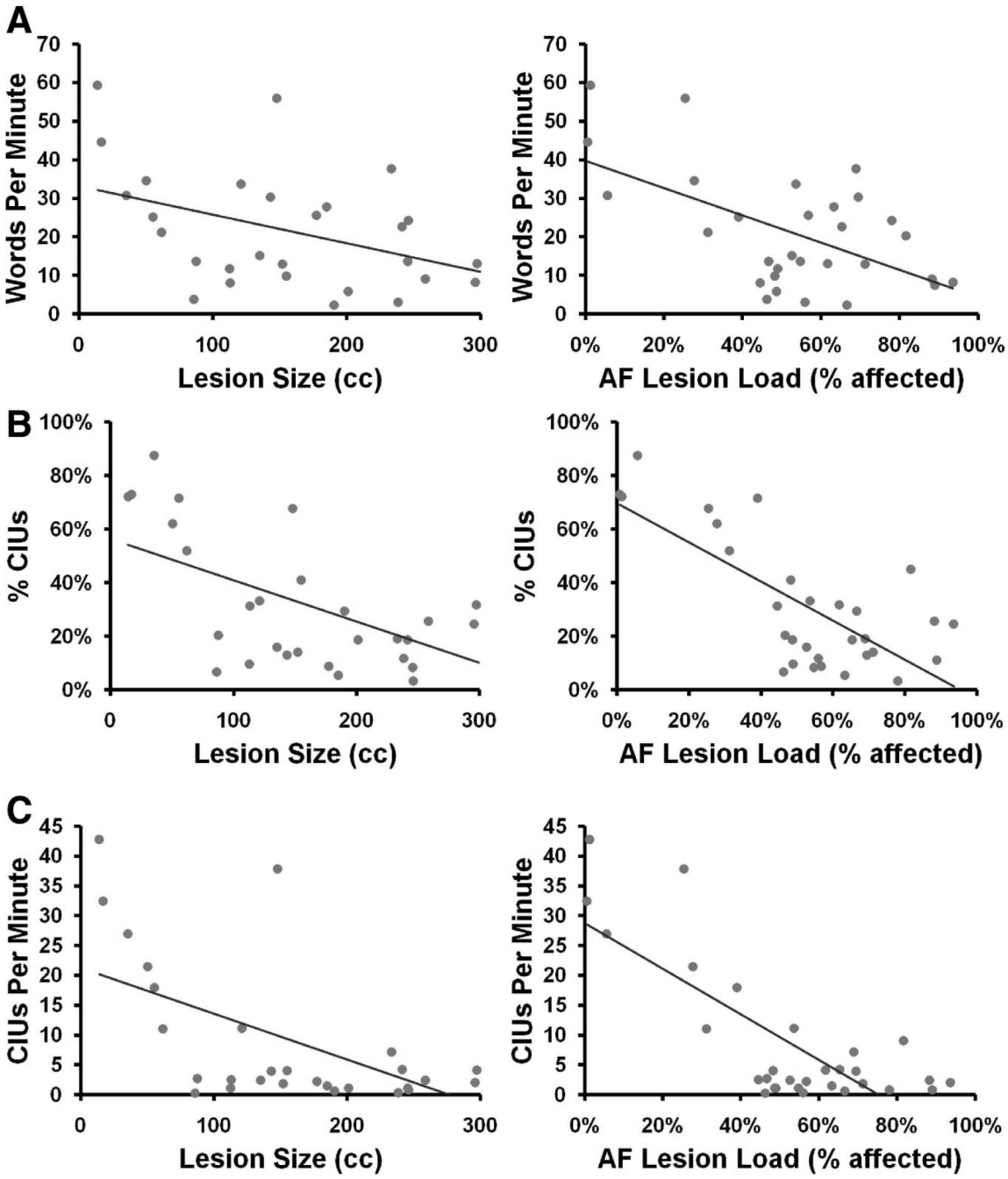

Figure 2: Regression analyses. Words/min (A); %CIUs (B); and CIUs/min (C) are plotted as functions of lesion size (measured in cc) and AF lesion load (represented as percentage of tract affected). CIUs indicates correct information units; AF, arcuate fasciculus.

Naming Ability

A final regression analysis was conducted using the same 4 variables to predict naming ability (adjusted R^2=0.417, P=0.001). AF lesion load (R^2=0.159, P=0.039) significantly predicted Boston Naming Test score, and UF lesion load displayed a nonsignificant trend (R^2=0.123, P=0.073). Neither EmC lesion load (partial R^2=0.069, P=0.187) nor lesion size (partial R^2=0.029, P=0.399) significantly predicted Boston Naming Test score.

Discussion

AF lesion load, but not EmC or UF lesion load, significantly predicted rate, informativeness, and overall efficiency of speech in patients with impairments of speech production after stroke. Lesion size, despite showing a substantial correlation with these lesion load measures, was shown not to be a significant predictor of speech production after stroke (Figure 3).

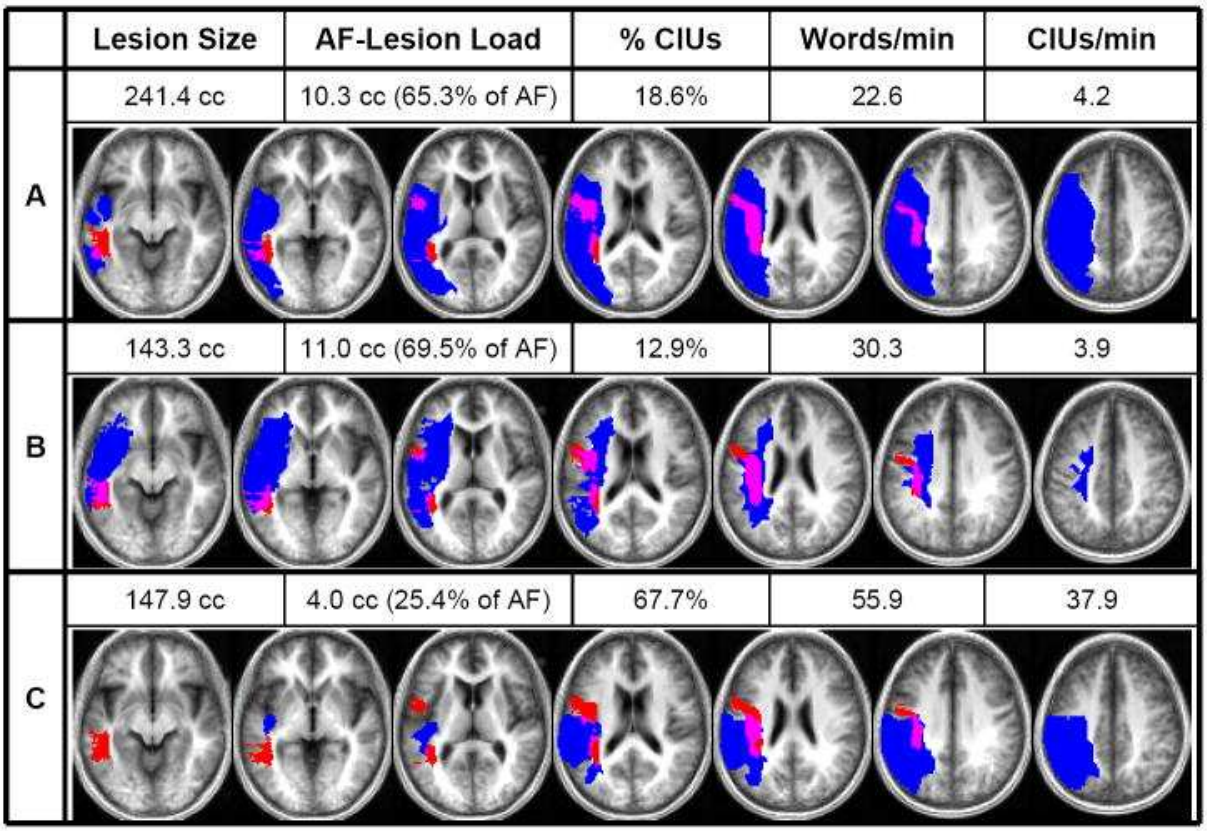

Figure 3: Lesion-diffusion tensor imaging fiber tract overlap. Shown here are examples of 3 patients' behavioral scores, lesion sizes, and AF lesion loads as well as their individual lesion maps (depicted in blue) overlaid onto the probabilistic AF map (depicted in red). Overlap between lesion and AF is displayed in purple. The axial slices depicted correspond to z=−10, −2, 8, 18, 26, 34, and 42 in Talairach space. Comparison of Patients A and B shows how 2 patients can display comparable AF lesion loads and behavioral scores despite drastically different overall lesion volumes. Similarly, comparison of Patients B and C shows how a similar lesion size can produce 2 markedly different AF lesion loads and, accordingly, result in very different levels of impairment. AF indicates arcuate fasciculus.

Our results are in accordance with previous lesion-behavior mapping studies indicating a critical role for white matter tracts in the production of fluent speech. In one such study (Naeser et la., 1989), CT images of 27 chronic patients were used to rate extent of lesion damage within specific regions on a scale from 0 (no lesion) to 5 (entire area has lesion). Although severity of impairment was not predicted by the amount of lesion damage in any single area, the

authors did report that extent of lesion within 2 subcortical regions (the subcallosal fasciculus and the middle third of the periventricular white matter) could, when used together, discriminate severely affected patients from mildly affected patients. It should be noted that the periventricular white matter contains fibers of the arcuate fasciculus, which we have examined in this study and associated with speech production. More recently, lesion-behavior mapping techniques have been used on a voxel-by-voxel basis to implicate white matter tracts in the production of fluent speech. In particular, studies have suggested involvement of the arcuate/superior longitudinal fasciculus to be related to impaired performance on the fluency subtest of the Western Aphasia Battery (Bates et al., 2003) and decreased word production during conversational interviews (Borovsky et al., 2007); however, the voxel-based lesion-symptom mapping method used in these studies does not allow differentiation between white and gray matter damage and their relation to speech impairment.

Despite the emergence of diffusion tensor imaging as a means of tracing white matter tracts in vivo and, as a result, a growing body of evidence for the importance of fiber tract integrity in fluent speech production (Breier et al., 2008; Hosomi et al., 2009; Schlaug et al., 2009), very few researchers have investigated the predictive value of lesion size and location with respect to major fiber tracts. Several studies have related speech and language impairment after stroke to the extent of lesion damage within specific cortical and subcortical structures (Breier et al., 2008; Hillis et al., 2004a; Hillis et al., 2004b; Parkinson et al., 2009); however, the aforementioned study by Naeser and colleagues (1989) remains the only one that has examined the relationship between white matter damage and impairment of speech production. In contrast to the qualitative nature of their investigation, our study is the first to quantitatively relate the extent of lesion damage within white matter tracts to verbal fluency.

Our results are of particular interest when considered in light the dual-stream framework of auditory language processing originally proposed by Hickok and Poeppel (2004). In this dualstream model, the dorsal stream, which is thought to be serviced by the AF, is responsible for the mapping of sound onto articulatory-based representations, whereas the ventral stream, includes the UF and EmC, is involved in the mapping of sound onto meaning (Leclercq et al., 2010; Saur et al., 2008; Friederici, 2009; Hickok and Poeppel, 2004; Glasser and Rilling, 2008; Parker et al., 2005). According to this model, speech rate should be more related to AF lesion load, whereas measures of semantic processing and function (e.g., informativeness of content) should be more related to UF and/or EmC lesion load. However, we found that all 3 of our measures were predicted by AF lesion load, but neither EmC nor UF lesion load.

Possible explanations might be that our measures do not purely reflect one neural circuit or

the other (e.g., WPM relies in part on retrieval of phonological word forms, although not as heavily %CIUs does). As a result, all of the behavioral measures may most strongly with damage to the most vulnerable tract of the 3 we considered. This tract is likely the AF. Furthermore, as was suggested by Hickok and Poeppel (2007) the dorsal stream (i.e., the AF) is more strongly left lateralized than the ventral stream and does not have the same degree of bihemispheric redundancy as the ventral stream. Finally, the AF mainly runs dorsal to the sylvian fissure, which is supplied by the superior division of the middle cerebral artery, and the region of the brain supplied by the superior division of the middle cerebral artery is the area most frequently affected by a stroke. Regardless of the explanation, our results highlight the critical role played by the AF in the feed-forward and feedback loops for the efficient mapping of articulatory-based representations onto phonemic representations (Guenther et al., 2006).

Although it has been suggested that the UF is important for tasks involving semantic processing such as naming (Lu et al., 2002), our results are in accordance with those of a recent study (Duffau et al., 2009), in which stimulation and resection of the UF in epileptic patients did not produce any deficits in performance on the naming subtest of the Boston Diagnostic Aphasia Examination.

In the future, automation of AF lesion load calculations may allow physicians and researchers to make more accurate prognoses regarding impairment of speech production after stroke and recovery potential, possibly even in the subacute stroke phase, and thus, identify optimal interventions for patients based on their lesion-behavior profiles.

Acknowledgments

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III Concluding Part

7 General discussion

The four papers presented in this doctoral thesis were part of a large ongoing project at the *Music, Stroke Recovery, and Neuroimaging Laboratory* in Boston (USA)[18], trying to assess the efficacy of MIT in a controlled clinical trial. The goal of the two presented fMRI studies was to examine the neural underpinnings of recovery in the chronic phase of stroke. While *Schlaug et al. (2008)* only presented two cases – one treated with MIT the other with the control therapy called SRT, *Marchina et al. (submitted)* introduce an entire group of 14 patients treated with MIT. Looking at this larger group, we were interested in the behavioral improvement and – measured with fMRI – the plastic changes in the brain associated with this intense MIT treatment. Beyond that, *Schlaug et al. (2009)* and *Marchina et al. (2011)* used DTI to examine structural white matter changes and furthermore related the language relevant white matter fiber tracts to each patient's lesionmap in order to explore the predictive value on performance.

The following chapters discuss different aspects and controversies raised by those studies, aim to put aphasia into a larger context of therapy in general, discuss specific aspects regarding MIT in particular (chapter 7.2), but first try to shed light on some methodological issues concerning the imaging techniques we adopted (chapter 7.1).

7.1 On methods

Over the last two decades modern neuroimaging methods such as fMRI and DTI have revolutionizoned the neuroscientific field which led to a growing number of new studies and innovative and changing software for anlysing the acquired data. Some software such as SPM is already well established, while others are newly developed or undergo changes and updates. Choosing the most suitable and reliable software, as well as evaluating new released programs is crucial for answering a specific research question. This chapter on methods addresses some of the issues, evaluations, as well as possible solutions or ideas that we had to deal with during the course of our studies.

[18] The laboratory is directed by Gottfried Schlaug, M.D., Ph.D. and located at Beth Israel Deaconess Medical Center and Harvard Medical School, Department of Neurology in Boston, Massachusetts, USA. For further information see www.musicianbrain.com

7.1.1 Methodological considerations regarding fMRI

Structural and functional neuroimaging using a 3-Tesla scanner is associated with a lot of loud noise from the switching of the gradient coils. Due to the use of auditory stimuli as well as overtly spoken responses for our study, we were confronted with the problem of how to avoid interference, masking or unrelated activation which would occur during continuous scanning paradigms. As explained in detail in chapter 5.1.3, we solved the problem by implementing a sparsed temporal sampling design which typically acquires a volume only every 15 seconds and thereby could avoid scanner noise during the presentation of the stimuli as well as the patients' responses.

Another scanner related issue we had to deal with was the immobility of many patients due to hemiparesis and the associated need for special transportation and help for getting into the scanner (wheel chairs are not allowed in the scanner room). Also, for a lot of these stroke patients – particularly the older ones – it proved to be difficult to lie still for the duration of the entire scan which normally took at least 1.5 hours. This resulted in a lot of movement artifacts in the functional as well as diffusion acquisitions which could not always be properly removed/reduced with the movement correction tools implemented in the SPM software we used.[19]

Apart from these more technical issues, there are a few other challenges to consider when dealing with stroke patients as subjects. Of uttermost importance is a very careful screening process of the patients beforehand, since a lot of them had previous surgeries where they were implanted stents, aneurysm clips, or other devices to help normalize the blood flow in or to the brain. Some of these devices may be magnetic and therefore incompatible with the strong magnetic field and possibly dangerous for the subject. We put a lot of emphasis on this process and always asked the patients for their detailed medical records which sometimes took a considerable amount of time and occasionally delayed the enrollment of the patient into the study.

7.1.2 Methodological considerations regarding DTI

During the course of my studies I worked with various DTI software, some based on deterministic others on probabilistic tractography algorithms. One study examining the plasticity in white matter tracts (Schlaug et al., 2009) used the software MedINRIA (Fillard et al., 2006) – a deterministic tracking method – for reconstructing the fibers and deriving fiber statistics of

[19] SPM software is freely available to the (neuro)imaging community on http://www.fil.ion.ucl.ac.uk/spm/

the tracts. MedINRIA is based on the Gaussian streamline tensor model and employs the tensorline propagation algorithm based on a local diffusion and tensor deflection approach (Weinstein et al., 1999). The ROIs were drawn by hand on the FA map based on prior anatomical knowledge in order to intersect the fasciculus of interest. For the traced tracts in our study one ROI was usually not sufficient, and additional ROIs were used applying a Boolean logic operator to the tract reconstruction (Conturo et al., 1999). This approach is only ultimately successful, if the person drawing the ROIs has a lot of skills and neuroanatomical knowledge. It has to be ensured that by placing the ROIs, the only tracts that pass the Boolean logic filtering process belong to the fasciculus of interest. Despite of this dependence on the operator, this approach can produce accurate reconstructions (e.g., Catani et al., 2002) and has proven to be useful in a range of applications (Catani and Thiebaut de Schotten, 2008; Epelbaum et al., 2008). Another problem we were confronted with was the fact that originally we were not able to normalize the brains due to the problem of aligning the tensors accurately. Only the most recent versions of MedINRIA have a registration tool implemented. Since we couldn't resort to this, we had to draw all the ROIs in native space which made the obtained results somewhat unreliable and hard to replicate, in spite of the fact that the same person drew all the ROIs according to the same protocol. Interestingly, in a recently published paper which compared and discussed 4 different streamline fiber tracking software – MedINRIA one of them – the authors regarded all the four tested software as unsatisfactory in fiber reconstruction due to a incomplete or incorrect anatomical portrayal of the chosen tract (Buergel et al., 2009). It is to state though that the authors of that paper used one particular approach to reconstruct the fibertract and the *cortico-spinal tract (CST)* was the only tract examined. Despite of all the disadvantages and weaknesses, MedINRIA is a great tool for exploration. The handling is all GUI assisted and very intuitive. The tracing of the fibers takes a fraction of the time which is used in probabilistic software and a tremendous advantage for exploration purposes is its beautiful 3D-image viewer with which the entire volume can be rotated, translated and zoomed. It has given me the opportunity to investigate the target fiber tracts and find the ideal set of ROIs for tracing them. Worth mentioning in this context is a very recent published paper by our group (Lindenberg et al., 2010) examining the CST in stroke patients before and after occupational therapy plus tDCS. Using MedINRIA Lindenberg et al. (2010) were able to discern an anterior (pyramidal tract) and a posterior (alternate motor fibers) part of the CST. This differentiation into pyramidal tract and alternate motor fibers was initially not possible using the probabilistic software FSL[20] but only after gaining expertise in MedINRIA

[20] Cf. http://fsl.fmrib.ox.ac.uk

Lindenberg et al. (2010) were able to draw the ROIs accordingly.

This touches another very important issue regarding fibertracking methods and their results. Finding new tracts with any DTI reconstruction software does not necessarily mean that there is an anatomical equivalent. It could merely be a statistical effect of the tracking algorithm. Given the amount of effort invested in developing and refining tracking algorithms, it is surprising how little has been done to attempt to compare those tract reconstructions obtained with non-invasive diffusion methods, with those obtained by classical neuranatomical dissection (Jones, 2008). An exception is a study which reported direct comparisons between 'virtual in vivo dissection' and classical neuroanatomical dissections (Lawes et al., 2008). Such trials are essential to gain a better understanding on accuracy and false negatives/positives (Jones, 2008). In our group we became particullarly aware of this problem when we tried to test our hypothesis that patients – due to large lesions on the left – use the right *inferior frontal gyrus (IFG)* to recover language function. Accordingly we were interested in testing whether there is a fiber connection between Broca's area and its right homologue. There is to date no anatomical study which would support such a connection, but in accordance with a recent study (Hagmann et al., 2006) we likewise found fibers running from pars opercularis and triangularis through the genu of the corpus callosum to their IFG-homologue areas.

FSL has many advantages over MedINRIA, such as its profound normalization tools or the better handling of crossing fibers; however, one must keep in mind that despite a growing number of ROI atlases, for a lot of the tracts the ROIs still have to be drawn by hand by an experienced rater, and the tracts, as well as the atlas ROIs, can be thresholded at an arbitrary level (Giorgio et al., 2010). Yet, there is no question that a probabilistic tracking method gives a much more realistic picture of the white matter structures than a deterministic method like MedINRIA. In conclusion, one has to be aware that tractography does not provide a direct measure of connectivity in the human brain although in certain circumstances it may provide information that is related to underlying cerebral connectivity. It is to wish, that as methods become more proficient, greater insights into the detail of the human brain structure can be obtained.

7.2 On therapy

After these considerations on methodological issues, the second part of the discussion which finally concludes my thesis provides a more detailed insight into the topic of aphasia therapy in general, MIT in particular and discusses different aspects and controversies raised by our and other studies in more depth.

7.2.1 Aphasia in the field of therapy

A general consensus exists that most of the spontaneous recovery in linguistic function occurs in the first weeks after stroke (Pedersen et al., 1995) and is completed by the end of the first year (Kertesz, 1984a, b), although reports exist which show improvements occurring as a result of long-term therapy of patients with chronic aphasia (Elman and Bernstein-Ellis, 1999; Pulvermuller and Schonle, 1993). A metaanalysis revealed that "the effect of treatment beginning in the acute stage of recovery is nearly twice as large as the effect of spontaneous recovery alone and that treatment initiated after the acute period achieves a considerably but appreciable effect" (Robey, 1994). There is no doubt that treatment even in the chronic stage of stroke can help aphasia patients regain speech. However, there are no universally accepted methods for the treatment of non-fluent aphasia against which new or existing interventions can be tested, nor have any criteria been established for determining treatment efficacy. Most interventions in the subacute phase are conducted by speech therapists who evaluate patients' individual needs, then use a combination of techniques to help recover language function.

7.2.1.1 An operational framework for aphasia therapy

An interesting operational framework which discusses neurological, cognitive, and metacognitive variables and processes important to treatment outcomes, implements aphasia therapies into a bigger picture which aims to help develop and select variable therapy programs for individual patients (Helm-Estabrooks and Albert, 2004). According to the authors, aphasia rehabilitation can be conceptualized as the process by which one attempts to close the gap between an individual's impairments and that individual's functional communication needs and desires. Standardized tests are used to identify levels of impairment in language and other cognitive domains ('cannot do') as well as spared abilites ('can do'). For establishing what the patient really does do, clinicans usually turn to observational measures. On the other side of the treatment equation are the 'needs' and 'wants' which are critical to treatment goal setting and accomplished by interviewing patient and family (see Figure 7.1 below).

In this context, the three above mentioned neurological, cognitive and metacognitive variables are of crucial importance. The *can/cannot do's* and the *needs* and *wants* are strongly dependent on what kind of neurological disorder (progressive/nonprogressive, seizures, etc.) a patient shows as well as on the site and size of the lesion. Furthermore the response to therapy and functional outcome is seriously influenced by the degree to which skills within the cognitive domain (attention, memory, executive functions, etc.) are spared or impaired. The importance of the cognitive skills was underscored by Hinckley et al. (2001) who stated that it was not

language scores, but rather scores obtained on cognitive tests such as the *Wisconsin Card Sorting Test* or the *Ravens Progressive Coloured Matrices* that predicted time needed to reach a certain performance criterion.

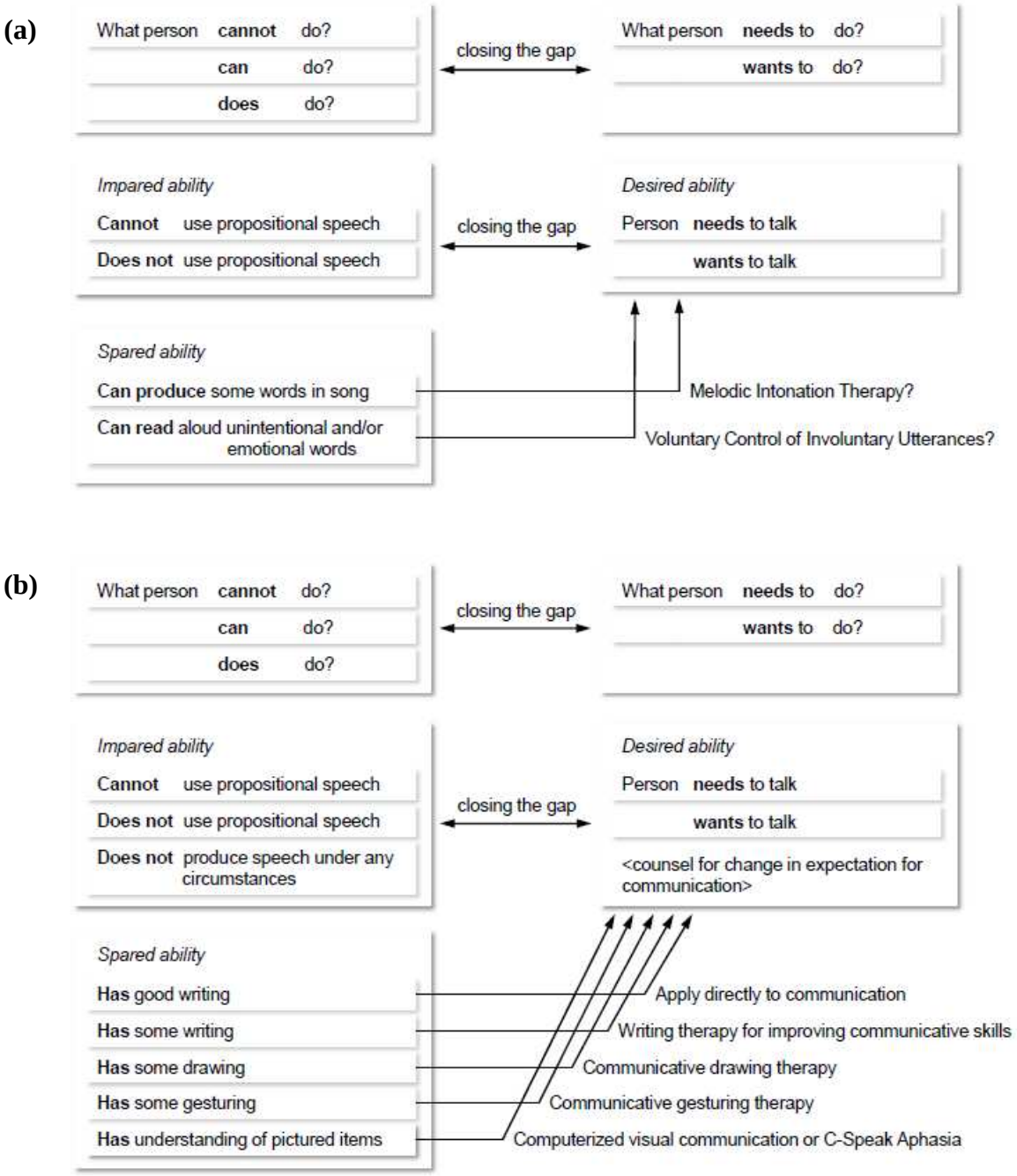

Figure 7.1: Aphasia rehabilitation: Working with assets (a) within and (b) outside the impaired speech modality (modified from Helm-Estabrooks and Albert, 2004).

In addition to cognition, Helm-Estabrooks and Albert (2004), the authors of that framework, highlight as well the importance of metacognitive processes for the treatment success. Among

these processes are *self-awareness and insight* (extent to which individuals possess an accurate, conscious representation of their functional disability), *motivation* (patients must understand why a task is being given, accept the importance of it and know that the work will have good functional payoff), *self-monitoring* (individuals attempt to correct of compensate for errors), *self-initiation* (ability to start or begin an intended action as opposed to responding refelexively to stimuli, important for independent use of skills), and *goal-oriented behavior* (setting, planning and executing set goals). Helm-Estabrooks and Albert (2004) tried to connect all of these aspects with their process approach to aphasia therapy.

In accordance with a specific neuropsychological assessment (Kaplan, 1988), this approach acknowledges the value of quantitative, standardized test scores as reference points, however it contends that in order to establish each individuals' strengths, weaknesses, cognitive styles and stragegies, one must go beyond the formal examination to probe, explore and record each patient's responses to a variety of stimuli and changes in task parameters.

This process approach can be viewed as an *asset approach* which stands in contrast to a deficit approach or the assumption that patients must practice what is hard to do until they get it right. Its goal is to develop or select appropriate aphasia therapy programs in which spared skills within an impaired language modality or a different modality are used as springboards for treatment.

7.2.1.2 Is practice intensity more important than the treatment type?

The optimal intensity of treatment is fundamental to the design and implementation of any treatment program for aphasia; however, unfortunately there is currently no standard definition of intensity. Irrespective of the treatment type, various authors have found that the intensity of treatment is an important component of therapeutic success (Bhogal et al., 2003; Brindley et al., 1989; Poeck et al., 1989; Robey, 1998). A review article by Bhogal et al. (2003) stated that while lower-intensity therapy provided over a longer period of time does not result in a significant change of outcome, a significant improvement can be achieved with more intensive treatment, delivered over a shorter period of time. However, a more recent review by Cherney (2012) states that the simplistic notion that 'more is better' is not necessarily supported by the evidence. Optimal intensities may vary depending on the type of intervention, the specific stimuli given and responses required of the participant as well as participant characteristics and environmental variables (Cherney, 2012; Cherney et al., 2011). Taken this together, we concluded that in our case intensive aphasia therapy delivered over 2 to 3 months is critical to maximize aphasia recovery. This is why we chose a high therapy-

intensity for our MIT study – treating each individual patient 1.5 hours/day, 5 days a week for 15 weeks in total.

Another interesting therapy method worth mentioning, which has intense therapy as its hallmark feature, and is together with MIT one of the most frequently studied approaches, is *Constrained Induced Aphasia (CIAT) or Language Therapy (CILT)* (Pulvermuller et al., 2001). Originally, CIAT was developed by translating Taub's successful *Constraint-Induced Movement Therapy (CIMT)* for hemiplegia (Taub et al., 1993; Taub et al., 1999) to chronic aphasia by applying the general principles to language training. The two most important principles of this treatment are the forced use of verbal language which requires that all responses provided during language treatment activities be constrained or restricted to the spoken modality and massed practice, which involves a high-intensity treatment schedule consisting of 3-4 hours of treatment per day for 2 weeks (Cherney et al., 2008). The goal is to progressively shape an improved linguistic behavior by using therapeutic language games. However, in the context of the previous mentioned research on therapy intensity (Bhogal et al., 2003), it cannot be ruled out that if any conventional therapy is used in massed practice fashion, it would lead to a pronounced behavioral improvement in a few days (Pulvermuller et al., 2001). Thus, in conclusion this suggests that CIAT might just be successful because of the intensity of the therapy and not necessarily because of the type of therapy. Nonetheless, it is a promising treatment as there is an observed improvement of language function within a short time and successful transfer of improved function to everyday life (Meinzer et al., 2007).

Unlike the studies using CIAT where the main principles were consistently applied and therefore the same intensity and length of therapy have been used (30 hours over 10 days), different groups studying MIT have unfortunately used vastly different amounts of treatment (see Table 7.1).

Study	Number of sessions/week	Total number of sessions	Session duration	Total time	Number of patients	Used Method
Belin et al., 1996	n.s.	n.s.	n.s.	4-450 weeks	7	PET
Bonakdarpour et al., 2003	3-4	15	n.s.	4 weeks	7	Behavioral
Wilson et al., 2006	2	8	n.s.	4 weeks	1	Behavioral
Breier et al., 2009b	2	6	30 min	3 weeks	3	MEG
Laine et al., 1994	3	42	45 min	14 weeks	3	SPECT
Strauss Hough, 2010	3	24	60 min	8 weeks	1	Behavioral
Schlaug et al., 2008;	5	75	90 min	15 weeks	2	fMRI
Marchina et al., submitted	5	75	90 min	15 weeks	14	fMRI

Table 7.1: Variablility in treatment designs used in various MIT studies.

An older study by Belin et al. (1996) included 7 subjects who received between 1 month and 9 years (~ 4-450 weeks) of treatment, but no further details about daily practice were given. Two other studies likewise only give information about how many sessions, but do not report how long the session lasted – one of them treated patients for 15 sessions (Bonakdarpour et al., 2003) and the other one 8 sessions (Wilson et al., 2006). Recently, Breier and colleagues treated their 3 patients two times a week each for 30 minutes across 3 weeks (Breier et al., 2009b). With three times 45 minutes a week for a total of 3.5 months, more therapy was given by Laine et al. (1994). A case study conducted by Strauss Hough (2010) applied 3 treatment sessions a week, each 1 hour for 8 weeks in total. Our study was – together with Laine et al. (1994) – the most intensive. We treated our patients for 15 weeks, 5 days a week (i.e., 75 sessions), 1.5 hours every day and session, respectively (Marchina et al., submitted; Schlaug et al., 2008). Overall, the large variability in treatment intensity used in the various MIT studies makes it difficult to draw conclusions about the quality and efficacy of MIT; this is in sharp contrast to the rather consistent approach in the CIAT studies.

Beside of CIAT and MIT there are a number of studies using various other approaches for treating aphasia which makes it – also regarding the treatment approaches as a whole – rather difficult to draw any conclusions about the quality of a treatment and even only about the improvement of patients. Furthermore, the pool of patients usually included many different aphasic syndromes and did not just concentrate on one particular which in itself could lead to different results. In the case of MIT approach there seems to be at least some clarity and existing guidelines on what the requirements for the ideal candidates are (see Table 7.2); however, there is not yet a clear evidence for the validity of this selection.

Candiates for Melodic Intonation Therapy
Cause of aphasia is unilateral, left hemisphere stroke, no right hemisphere involvement
Non-fluent or severely restricted verbal output, that may be restricted to nonsense stereotypy
Relatively good auditory comprehension
Poor repetition, even for single words
Able to produce some real, accurate words when singing familiar songs
Poor articulatory agility
Good emotional stability, motivation, and attention span

Table 7.2: Ideal candidates for MIT according to Helm-Estabrooks et al. (1989).

Last but not least there are no real large clinical aphasia therapy trials which include a sufficient number of subjects in order to draw conclusions about the efficacy. This is as well the case in the field of MIT; here most studies are either case studies or use only a very few patients (see Table 7.1). Our study is up to date probably the largest clinical trial not only trying to assess the efficacy of MIT, but furthermore compare it to a matched control treatment that does not include the unique elements of MIT (see Marchina et al., submitted; Schlaug et al., 2008).

7.2.2 Therapy effect and outcome measures for aphasia studies

Irrespective of the used treatment method, most aphasia studies measure the improvement or language outcome with one or several tests such as repetition or naming tasks of any common aphasia battery. They have the advantage of providing a widely accepted and standardized speech outcome measure, they are relatively quick to collect, easy to score and give an idea about patients' performance or progress in different language modalities. However, for more information about the quality and spontaneity of a patient's ability to entertain a conversation, the collection of a propositional speech measure – which is usually only a very small part of these batteries – is indicated. The term 'propositional speech' is often used in contrast to 'automatic speech' or 'nonpropositional speech'. In one of the very difficult to find definitions of these terms, *nonpropositional speech* is described as ready-made utterances that may express emotion but are "intellectually dead," while *propositional speech* is an intentional expression of thought (Jackson, 1915). While automatic speech consists of over-learned sequences (e.g., counting, days of the week) and commonly used phrases (e.g., "Thanks a lot," curse words), propositional speech is more communicative and novel. People with aphasia can often produce fluent segments of automatic speech but are unable to produce much propositional speech (e.g., shortly after a stroke, patients can only say very little and are pretty much at the single-word level in terms of propositional speech, however they can pick up the phone and say "Hey, how's it going?" perfectly). From a linguistic perspective, automatic speech is so over-learned that we can access it in 'chunks' and go right from the semantics to, probably, the associated articulatory commands for the whole chunk. In contrast, propositional speech requires formulation and, therefore, an – at least somewhat – intact linguistic system (to retrieve the words, put them into some sort of syntactic frame and retrieve the articulatory commands). Tests which assess propositional speech are more laborious as they need to be transcribed and scored by a qualified person which might be the reason why many studies prefer other speech outcome measures. Nicholas and Brookshire (1993) address this problem

in their paper by stating that analyses of the connected speech of adults with aphasia have focused primarily on how their speech conforms to standard language rules and patterns rather than how well it communicates information to listeners. They note that there is a scarcity of standard measures for characterizing this aspect of connected speech for clinicians and investigators who want to quantify changes in the informativeness of the connected speech of adults with aphasia in response to treatment or in response to manipulation of experimental variables. Taken this as basis, Nicholas and Brookshire (1993) described a standardized rule-based system for quantifying the informativeness of connected speech elicited with a variety of stimuli called *Correct Information Unit (CIU).* Included in the CIU counts are accurate words, which have to be relevant, and informative relative to the eliciting stimulus, however, they do not have to be used in a grammatically accurate manner to be counted. Each CIU consists of a single word, and only words that are included in the word count can be counted as correct information units. In order to derive the CIUs from spontaneous speech, a standard narrative production task such as the cookie theft, interviews/conversations with open-ended questions and a naming task may be utilized (Nicholas and Brookshire, 1993).

We have chosen to use CIUs/min as our primary outcome measure and there is a great deal of literature to support this choice (see Brookshire and Nicholas, 1994; Nicholas and Brookshire, 1993; Prins and Bastiaanse, 2004; Saffran et al., 1989). Although a typical patient undergoing MIT initially has very limited verbal output, results of our pilot trial and other reported case series (Bonakdarpour et al., 2003; Sparks et al., 1974) show that this spontaneous speech output can increase by more than 100% over the course of treatment. Thus, while patients' pre-therapy speech output may be limited to words/phrases with few syllables, their post-therapy output is likely to include a greater number of syllables per phrase and in some cases, simple sentences. Despite the extensive body of literature on the impairment of spontaneous speech output, from a linguistic point of view it remains difficult to analyze and quantitatively describe discourse production, and there are no universally accepted methods available (Prins and Bastiaanse, 2004; Prins et al., 1978; Saffran et al., 1989; Shapiro et al., 1993; Thompson et al., 1997).

Using this type of speech outcome measure led to some difficulties in the process. *Firstly*, the picture description and the interview needed to be orthographically transcribed and scored by an experienced person – preferably a speech-language pathologist who follows a strict protocol in order for the outcome to be adequate and a reflection of the patients' improvement. This is a rather time consuming endeavor and in addition sensitive for rater dependency. Although Nicholas and Brookshire (1993) reported high interrater reliability, the scores are more varia-

ble than by using very standardized tests as found in aphasia batteries. *Secondly*, the measures need to be timed in order to calculate the three reported outcome measures: 1.) words per minute, 2.) percent of words that were correct information units and 3.) correct information units per minute, the time, word and CIU count was used. However, for non-fluent aphasic patients to answer a question e.g., about how their stroke happened can be very challenging, hence most of them needed time to get started and say something at all. This time occasionally exceeded the given minute, even though the patient was actually able to say several CIUs. In order to capture the patients' performance more accurately we experimented with the scoring system and introduced a 'movable' minute. Nicholas and Brookshire (1993) also note that the three calculated measures provide information about the efficiency of connected speech, although neither percent CIUs nor words-per-minute alone will give a complete picture of a speaker's efficiency. Overall, this speech outcome measure is not very often used in aphasia therapy and neuroimaging studies. Beside of our group, only Breier et al. (2009b) have used CIUs, however they calculated them from a set of MIT phrases. The few other conducted MIT studies mostly used subtests from aphasia batteries as outcome measures as mentioned at the beginning of this chapter.

7.2.3 Brain plasticity in post-stroke aphasia: the role of the hemispheres

Current thinking about neuroplasticity suggests that there are at least four major kind of potential neuroplastic changes that may account for recovery operating at the representational module level (Grafman, 2000). These include homologous area adaptation, cross-modal reassignment, map extension, and compensatory masquerade. In the specific case of aphasia language recovery, there is evidence for both homologous area adaptations in right hemisphere and map extension in perilesional left hemisphere regions (Thompson, 2000). However, to date the extent to which such observations reflect processes of neuroplasticity is not entirely clear. There is the possibility that such observations instead reflect large-scale neural networks that serve language even under normal conditions at least in some individuals (Thompson, 2000). The role of the right hemisphere in the recovery from aphasia is controversial and has been discussed up to this day by aphasiologists and neuroscientists. Smith (1966) described a left hemispherectomy patient who was able to sing and showed slow recovery of language functions during the next seven months following surgery. He concluded that the right hemisphere has considerable capacity for language. This hypothesis was tested by staging serial, unilateral, intracarotid amobarbital tests on two right-handed aphasic patients (Kinsbourne, 1971). Arrest of vocalization occurred with right-sided but not left-sided injec-

tions which were interpreted as evidence that dominance for language had shifted to the right hemisphere. Mazzocchi and Vignolo (1979) described a patient who became aphasic following a left *cerebrovascular accident (CVA),* recovered language function after 6 months of treatment, but a second CVA in the right hemisphere resulted in severe Wernicke's aphasia with pure word deafness. The authors state that these findings "strongly suggest that recovery of language after the left hemisphere lesion was due to functional compensation by the right hemisphere" (Mazzocchi and Vignolo, 1979). Geschwind (1972) already suggested a strong involvement of the right hemisphere in the development of language processes. He notes in a discussion about childhood aphasia that the right hemisphere learns language along with the left, and that recovery is not so much a matter of relearning by the right hemisphere, but rather an assumption of responsibility for language functions that previously had been controlled by the dominant left hemisphere. He added that "really effective rehabilitation of the adult aphasic depends on the possibility that he, like the child, has language learning in the other hemisphere which for some reason he is not capable of using. […] Perhaps some way could be found to 'attack' the right hemisphere of the adult in order to make the latent language learning become manifest" (Geschwind, 1972, cited in Albert et al., 1973).

The issue of right hemisphere assumption of language skills following aphasia is of particular relevance for MIT which uses a singing and intoning approach. There is evidence that some musical tasks and/or musical stimuli appear to activate brain regions that overlap with areas that are engaged during language tasks (Gaab and Schlaug, 2003; Koelsch et al., 2002; Ozdemir et al., 2006; Patel, 2003; Patel et al., 1998). In particular, tasks targeting the perception of musical aspects that require a more global than local processing strategy (e.g., melodic contour, musical phrasing and/or meter), tend to elicit greater activity in right than left-hemispheric brain regions. Similarly, patients with right-hemisphere lesions have more difficulty with global processing (e.g., melodic processing) than those with left-hemisphere lesions (Peretz, 1990; Schuppert et al., 2000). A depression of the ability to sing the melody of well-known songs after sodium amobarbital has been injected into the right carotid artery has been reported (Bogen and Gordon, 1971). Since MIT incorporates both melodic and rhythmic aspects of music (Albert et al., 1973; Cohen and Ford, 1995; Cohen and Masse, 1993; Sparks and Holland, 1976), it holds a unique position among therapies in its potential ability to engage language-capable areas in both hemispheres. MIT may exert its effect by either unmasking existing connections between music and language-capable brain regions in both hemispheres, or by engaging preserved language-capable regions in either or both hemispheres. The developers of MIT proposed in one of their early papers (Albert et al., 1973) that MIT

facilitates the use of language by the non-dominant right hemisphere, which had been suppressed by the dominant left hemisphere, in spite of the fact that the dominant hemisphere was damaged. If this suggestion is correct it would imply that the right hemisphere has language areas which perhaps are not fully utilized under normal conditions. The question of how much the right hemisphere contributes to recovery of language in aphasic patients has been the focus of a variety of investigations. Nevertheless, the answer has been elusive. With the advent of fMRI investigators of poststroke aphasia believed that this new method would transparently reveal the brain areas that assume language functions of the damaged brain. But different studies showed divers results. While some studies suggested that left hemisphere perilesional areas would assume lost language functions in individuals who had partially recovered language (Heiss et al., 1999b; Karbe et al., 1995; Thiel et al., 2001; van Oers et al., 2010; Warburton et al., 1999), others insisted on right hemisphere homologue regions to compensate for the lost function (Musso et al., 1999; Ohyama et al., 1996; Raboyeau et al., 2008; Richter et al., 2008; Thulborn et al., 1999; Weiller et al., 1995). Some studies presented results which indicate regions in both hemispheres to regain the lost language functions (Breier et al., 2009a; Pulvermuller et al., 2005; Rosen et al., 2000; Winhuisen et al., 2005). It is important to note that some investigators are convinced that the activation on the right hemisphere is the expression of a 'maladaptive strategy' and that this activation rather reflects disinhibition rather than functioning of the right frontal areas due to infarction of left frontal areas (Martin et al., 2004; Naeser et al., 2005b; Thompson and den Ouden, 2008). All these conflicting results were at least to some degree reconciled in a study by Saur et al. (2006) whichs suggests that reorganization during language recovery proceeds in three phases: A strongly reduced activation of remaining left language areas in the acute phase is followed by an upregulation with recruitment of homologue language zones, which correlates with language improvement. And thereafter, a normalization of activation is observed, possibly reflecting consolidation in the language system. This finding confirms an earlier study by Knopman et al. (1984) which provides evidence for participation of the right hemisphere in language comprehension in recovering aphasics, and for later return of function in left hemisphere regions that may have been functionally impaired early during recovery.

In the MIT study conducted by our group (Marchina et al., submitted), which includes a group of 14 non-fluent chronic aphasia patients, we see a clear shift of the activation to the right hemisphere. When reviewing the lesions of our patients it becomes obvious, that all of them had large lesions in the left hemisphere which damaged extensive parts of the perisylvian language network. As already suggested by some authors (for reviews see e.g., Lazar and

Antoniello, 2008; Marsh and Hillis, 2006), lesion size and location might be a crucial factor to whether or not the reorganization of language function rather occurs in the left perilesional or right homologue areas. Karbe et al. (1998) summarizes this nicely in conclusion to his study by stating that the restitution of the left superior temporal cortex determined the long-term prognosis of aphasia. The brain recruited right-hemispheric regions for speech processing when the left-hemispheric centers were permanently impaired, however, this strategy was significantly less effective than the repair of the original speech-relevant network. Marsh and Hillis (2006) offer three plausible (and nonexclusive) explanations for this right-left-hemisphere contradiction. *First*, it has been proposed that right and spared left hemisphere regions contribute to recovery, but location and extent of recovery depend on factors such as the extent of the left hemisphere damage, the duration of the injury and which language functions are affected (Hillis, 2005; Hillis et al., 2002). *Second*, both hemispheres are involved in the recovery process. Although most studies acknowledge that in the recovering brain there is increased activation in both right language homologue and left perilesional areas, varying degrees of significance are attributed to these two forms of activation. *Third*, it was proposed that following stroke, language initially switches to the contra-lateral hemisphere, until the left hemisphere areas can be reintegrated into the language network (Heiss et al., 1999b; Rosen et al., 2000; Small et al., 1998).

Only very recently, a new study by Baumgaertner et al. (2012) testing healthy subjects offered a complementary explanation for right hemispheric activation during language processing, namely increased perceptual processing of nonlinguistic features of language stimuli. This interpretation is in line with another study which suggests that right-hemispheric activation after left-hemispheric stroke may reflect an up-regulation of nonlinguistic cognitive processing (van Oers et al., 2010)

The question remains what the right hemisphere activation and the persilesional activation represent, respectively. Some authors suggest that the activation on the right hemisphere in left lesioned brains probably reflects the adoption of a new, less efficient strategy by the right hemisphere (e.g., Rosen et al., 2000). This fits well with the theory that the right hemisphere is capable of performing some but not all the language tasks, e.g., semantic info is processed by the right, while orthographic to phonologic conversion is rather a left-only process (Saffran et al., 1980). Alternatively there could be a loss of mechanisms that normally regulate the right hemisphere's level of activation, when the left hemisphere is damaged (Kinsbourne, 1971). This would explain the lack of correlations to performance in patients with right hemisphere activation and left-sided lesions. Unfortunately, regarding correlation between lan-

guage performance and level of activation as determined by imaging techniques, conflicting results have been reported (Belin et al., 1996; Heiss et al., 1999b; Karbe et al., 1998; Rosen et al., 2000). Some authors did present a correlation between performance and the degree of activation in the right hemisphere (Noppeney et al., 2005). This aligns well with results of our own study (Marchina et al., submitted) which demonstrates a significant positive correlation between language outcome measure and an anatomical region of interest (ROI) in the inferior frontal cortex.

Additional evidence supporting speech recovery through the right hemisphere comes from DTI studies. Several authors have demonstrated a leftward asymmetry of the arcuate fasciculus (AF) – the fiber bundle that connects language relevant regions in the inerior frontal cortex with the posterior temporal lobe – in healthy control subjects (Nucifora et al., 2005; Vernooij et al., 2007; Glasser and Rilling, 2008). In the case of our stroke patients, we were not able to trace the AF on the left hemisphere for any of them due to their large lesions, but the right AF was detectable in all of them before and after receiving intensive MIT. Our results suggest an upregulation of the AF due to the intensive language therapy (Schlaug et al., 2009). Corresponding to this DTI outcome, our fMRI study shows post therapy a stronger right perisylvian network of activation in regions which are served by the right AF (Marchina et al., submitted). Despite these findings it appears that there is slightly more evidence for a better recovery by integrating brain regions around the lesion although it is not exactly clear how capable these regions are in terms of compensating for lost functions. Some propose that in small strokes, areas around the lesion correspond to areas that are normally active in language and activation is simply the restoration of normal function, not actual remapping (Heiss et al., 1999b; Nudo et al., 1996). When areas around a lesion show increased activation over time, these left hemisphere areas may be taking on new functions or being reperfused and thereby restored to their normal function. It has been shown that the recovery process in the acute phase can be boosted by treatment and that the effect is nearly twice as large as the effect of spontaneous recovery alone (Robey, 1994). This might be an additional indication for the brain's capability of restoring its function on the left hemisphere. The specialization of the areas around the damaged tissue could play a role in a possible shift to the contralateral side. If the tissue that surrounds the lesion plays an active role in language, it is more likely to assume lost language functions, however if the tissue that surrounds the lesion cannot become part of the new language network, language processing is likely to shift to the right hemisphere (Marsh and Hillis, 2006).

Taken together it is at this point still unclear whether language shifts to the right hemisphere

in aphasic patients or not. Reaching a definite conclusion about which hemisphere is responsible for language recovery may also be difficult because of a variety of influencing factors, such as which specific language functions were impaired by the stroke, which functions were recovered, what parts of the brain were damaged or spared, how specialized the damaged area of the cortex is, the degree of localization of the language function recovered, and what parts of the brain normally participate in that language function are involved (Hillis, 2002).

7.2.4 MIT in the context of music therapy

"The brain that engages in music is changed by engaging in music."

Michael Thaut

The traditional duality of music and language as different psychological faculties is reflected in older theories about the lateralization of speech and music where speech functions were thought to be localized in the left and music functions in the right hemisphere of the brain (Jancke, 2012). However, new findings from modern neuroimaging techniques show that music and speech functions have many aspects in common and that certain neural modules are similarly involved in speech and music (Tallal and Gaab, 2006). Even though the developers of MIT might have based the therapy more on the traditional view, these new findings of a common network for music and language could at least partially be responsible for the positive effect of MIT on behavior and brain plasticity as shown by the results of our studies (Marchina et al., submitted; Schlaug et al., 2009). Evidently, speech functions can benefit from music functions (and vice versa) and music seems to have a strong influence on brain plasticity which is why it can be used as a non-invasive tool for neuropsychological and neurological therapies (Jancke, 2009a).

The understanding of the role of music in therapy and medicine is still undergoing a rapid transformation. The reciprocal relationship between studying the neurobiological foundations of music in the brain and how musical behavior through learning and experience changes brain and behavior function has been discovered over the past 15 years by connecting the fields of neuroscience, music cognition, music therapy, and rehabilitation (Thaut, 2005a). This connection has been established through the demonstration of experience-dependent plasticity of the brain which is powerful in helping to increase the understanding of learning, cognition, and therapeutic rehabilitation. Recent findings suggest that music can stimulate complex cognitive, affective, and sensorimotor processes in the brain which can then be generalized and transferred to nonmusical therapeutic purposes (Thaut, 2005a). During the last few decades, a more systematic music-speech relationship has formed in the clinical and re-

search literature. Both music and speech have long been thought to have common roots in human evolution, with music usually being thought of as an offspring of speech (Thaut, 2005a). Due to the many similarities between music and speech, it has often been assumed that music − and especially singing − is a valuable tool for the treatment of speech disorders. Despite of the fact that there is an extensive literature in music and speech therapy, many of the earlier papers frequently were not data-based or did not employ the most stringent research methodologies (Galloway, 1975; Thaut, 2005b).

According to Thaut (2005b) music, speech, and language share from a biomedical perspective two important functions: 1.) the aural and production features shared by spoken language and musical vocalization in singing, and 2.) the ability of both systems to embed communicative functions in the auditory modality. The notion that music may help language and speech functions is found in many records throughout human history. In the light of the emerging database in clinical and basic science, and analyzing the function of musical stimuli in the therapeutic process, Thaut (2005b) distinguishes at least four distinct underlying mechanisms which are worth mentioning, as they are of relevance for MIT and the attempt to explain why singing and MIT, respectively has the potential to facilitate word or syllable production:

1. *Differential neurologic processing of music and speech*. The neural circuitry for music and speech, especially in regard to singing, is neuroanatomically partially overlapping and partially separated. Shared and parallel processes may allow flexibility in facilitating neuroanatomical reorganization or accessing alternative pathways of function in case of focal brain lesions.
   ► Much of the prevalent rationale for the causative mechanisms of melodic intonation therapy is built on this concept.
2. *Rhythm and timing*. The effects of auditory rhythm on speech rhythms, fluency, rate control, intelligibility, articulatory control and respiratory function are documented for a variety of clinical applications.
   ► This is implemented in MIT through rhythmic anticipation: the use of syllable tapping with the unaffected hand during MIT may further facilitate the use of right-hemispheric executive and motor control systems for verbal production through rhythmic anticipation or rhythmic entrainment (Thaut et al., 1999).
3. *Commonalities between speech production and vocal production in music*. The shared modality of aural communication allows for transfer effects of therapeutic exercises using music to enhance therapeutic goals in speech production.
   ► In MIT this transfer effect has been tried to achieve through the reduction of speed: in

singing, words may be articulated at a slower rate than in speaking thereby reducing the left-hemisphere advantage. Another process is syllable lengthening: the acoustic correlate of speed reduction in singing helps non-fluent aphasic patients become more fluent, and may be supported more by right-hemispheric structures. And last but not least to mention syllable 'chunking': prosodic features (e.g., intonation, change in pitch, syllabic stress) may help patients group syllables into words and words into phrases, and such 'chunking' (Chase and Simon, 1973; de Groot, 1965) may also enlist more right-hemisphere support.

4. *Auditory-based communication systems.* The linguistic components in speech − phonology, prosody, syntax, and pragmatics − all have counterparts in musical structures. The major difference arises in the referential semantics of language which is not shared by music. Even though music can acquire referential meaning, the sound patterns of musical language initially communicate their meaning through the relationship between the elements of the patterns themselves. Through these shared language processes of the two communication systems, music has been used successfully to enhance and facilitate speech and language development.
   - ► MIT takes advantage of this fact by intoning or singing words and phrases which does not just activate language regions but in addition makes different aspects of the 'musical system' in the brain available. This interaction of the two systems is beautifully expressed in the famous observation that non-fluent aphasics are able to sing the lyrics of a song, but cannot speak them (Gerstman, 1964; Geschwind, 1971).

In summary, concurrent with Thaut's suggested mechanisms (Thaut, 2005b) one could say that the elements important for the facilitating effect of MIT might be the slower production rate in sung than in spoken language, the prolonged voicing patterns, the predictability of speech sound encoding based on an external timing plan, the use of a differential pitch system in singing (Natke et al., 2003), the handtapping which leads to rhythmic entrainment and finally the affective components of music connected to emotional arousal circuitry which in turn may facilitate speech circuitry activation (Patel, 2003). Thus, music provides a stimulus that substitutes for compromised internal functions, accesses compensatory networks in the brain, and may help build new pathways shaping the plasticity of the brain.

7.2.5 Computer therapy: the future in aphasia therapy?

A very novel and young approach for aphasia treatment assembles computer technology. It is usually used in people who are in the chronic stages of aphasia. Because most language im-

provement occurs within the first few months following stroke (Mimura et al., 1998), much of the attention and effort of clinicians are directed toward maximizing improvement during this acute period. In the chronic phase recovery is much slower and the rate of change is markedly less than during the acute phase (Hanson et al., 1989). This reduction in potential for recovery over time consequently requires more time and resources during the chronic than during the acute phase. Furthermore, resource constraints force to focus treatment efforts on the acute and limit access to therapy during the chronic phase (Katz et al., 2000). Computerized therapy is less costly than clinician provided therapy and can therefore serve as an effective source of stimulation and instruction for patients during the chronic phase of aphasia (Wertz and Katz, 2004).

In an excellent review by Katz (2010), three fundamentally different ways how computers are used in aphasia rehabilitation are presented: First, *alternative and augmentative communication (AAC)* devices and programs maintain or improve functional communication through the use of a device or computer program that aids conversation. Some of these devices can be very sophisticated and patients improved on the particular tasks which were being used, however, the natural language was not affected when the program was not being used. Furthermore, due to problems understanding others, monitoring their own output or operating the devices while trying to share the burden of conversation, many aphasics are unable to use AAC devices effectively. This makes them a somewhat limited solution for improving chronic aphasia patients' communication problems. The second strategy called *computer-assisted treatment (CAT)* is presented on a computer as the patient and clinician work together on the program. The role of the computer is limited to supportive functions and clinician retains the traditional responsibility. This advantage of the approach is its flexibility because a clinician, unlike a computer program, can respond to unanticipated or subtle problems with solutions that are nuanced, novel, and creative.The downside is its dependency on the clinician which makes it inflexible for the patient. This problem is addressed in the third method as *computer-only treatment (COT)* which is designed to allow patients to practice alone at the computer, without simultaneous supervision or direct assistance from clinicians. These programs can be adaptive and alter elements of the task in response to the patient's performance or simulations of real-world interactions can be created. However, since a designer cannot anticipate all possibilities, the intervention might be too simplistic and inflexible to a certain degree. Despite of all these limitations, COT has clear advantages: patients can engage in interactive treatment activities more often and for longer periods of time, and the treatment is not restricted by the clinicians schedule which gives aphasics more control over their lives, increasing participa-

tion in their own rehabilitation by having the choice of when, where and what to practice (Katz, 2010).

For people with chronic aphasia factors such as motivation, dependency, and quality of life become increasingly important as recovery slows (Ross and Wertz, 2003). Also under conditions of perceived helplessness and hopelessness, people commonly become depressed (Code and Herrmann, 2003) and have greater difficulty coping with and adapting to changes and problems (Coelho, 1974). Having options and responsibilities can create a strong, positive effect on the well-being of this people in otherwise dependent situations. That is why Wertz (1981) advocated that patients in therapy maintain as much independence as possible and that a long-term goal of therapy is to have patients become their own best therapists. Through insights which patients develop over time regarding their problems and strengths, they are empowered to take a unique and active role in their recovery. The independent use of computers is one opportunity to allow patients to fill that role (Katz, 2010).

Referencing it as a concrete example falling into the third category discussed above (i.e., COT), one recently published research study introduced IMITATE therapy, a computer-assisted system for aphasia therapy based on action observation and imitation (Lee et al., 2010). It consists of silent observation of audio-visually presented words and phrases spoken aloud, followed by a period during which the participant orally repeats the stimuli. According to the authors, the therapy is based on the neurophysiological evidence of mirror-neurons with visual and motor properties that discharge both when an action is performed and during observation of the same action (Kohler et al., 2002; Rizzolatti et al., 1996). Lee et al. (2010) postulate that behavioral stimulation of this parietal-frontal mirror neuron system may play an important role in motor learning for speech and thereby aid language recovery after stroke.

Such an application in mind, MIT is also a therapy method which has undoubtedly the capacity to be implemented as a COT. Even though we have not planned and conducted a clinical trial in our group yet, we nonetheless designed a simple practice system, based on the MIT principles. Patients log in to a protected website that displays practice videos for individual patients. Each of the three levels of MIT was video recorded directly opposite from the therapist, so that it appears to the viewer as if they are a participant in the session. Each target phrase is presented with the visual cue card and the therapist guides the patients through the steps appropriate to each level – leaving time for the patient's response at each step. The video screen is designed so that patients can replay target phrases on which they need more practice or move on to the next phrase. In addition, each time patients log in, a log file of their practice time is generated and patients are able to access and view records online that lists the

date and practice time.

Patients receive the login for the program and can conveniently practice from home. The disadvantage is that we have no control of whether or not the patient's response was accurate or not. This is somewhat a shortcoming as aphasics very often do not realize whether what they said was correct or not. There is a mismatch between their perception and their action. As a consequence they might practice something in an incorrect way and build a routine that has to be unlearned or corrected afterwards which is usually a lot harder than learning it the correct way the first time. To counteract this to some degree, our patients only get to practise with that system when they have developed the ability to critically listen to their own speech output, such that they can determine which parts of their output matches the target phrase and which is not. This means in the context of the study that all the patients receive first a certain amount of MIT before being able to use the computer practise system. Only a few patients have used the system so far and we have not yet collected any quantitative outcome measures of improvement. However, this is just a starting point and it might be an interesting study to conduct in the future as there is a huge demand for treatment, but most people cannot afford expensive treatment with a therapist. Due to the fast developing digital technologies and a large interest and demand from patients and their relatives, the most recent challenge we have undertaken is the development and design of smartphone app in the style of MIT. Since more and more people own a smartphone and unrestricted internet access is available almost everywhere, it has become even easier and handier for aphasia patients to practice wherever they go. This project with the working title "MIT on the go" however, is still very much in the beginning stages.

7.3 Practical implications for the future

Reaching a better understanding of the recovery mechanisms and plastic reorganization of the brain following injury is still an ongoing process, which undoubtedly will empower researchers and investigators to design improved treatment methods for their patients. In this context it is of importance to consider the opportunities and strengths as well as the pitfalls and shortcomings of the methods used to identify neural substrates that underlie language and the recovery of language functions, and to realize that a single study can only answer a limited number of questions and that there is a need to have converging evidence from various functional, structural imaging and lesion studies. Accordingly, our project comprises several studies using various techniques and is so far probably the largest clinical trial trying to assess the efficacy of MIT by examining the effect of the therapy across a MIT patient group. Further-

more, we have a large group of patients who underwent the control SRT and a group of well-recovered aphasia patients as well as a group of not treated aphasic controls which we aim to compare to the MIT group in the future. All patients – independent from therapy – underwent language assessements and the fMRI protocol at least once after enrollment into the study. The healthy control subjects only performed the fMRI task. In addition to the extensive language assessments and the functional imaging data, we also collected DTI data for all the subjects. This project has become very large and it will take a lot more time in the future to finish up, as it still holds endless possibilities to analyze and compare the data, which is beyond the scope of my doctoral thesis. However, taking into account that most of the previous MIT studies used relatively small subject samples or were case studies, and the amount of therapy was hardly ever as intense as suggested by the authors who developed MIT, one can hope that this study will become a landmark study which not only leads to valuable insights that can be used for future studies, but more importantly leads to fruitful implementation of the therapy in aphasia rehabilitation programs.

An important aspect which is often mentioned, but not seriously realized is the transfer of the theory and the research into the practical. Research is busy conducting studies, publishing data and applying for new funding for future studies. However we are often negligent of the fact, that particularly in stroke recovery research, the knowledge and findings we acquire is very important for a lot of stroke patients. Since there is no cure for stroke and brain cells – at least to date – cannot be replaced, a stubstantiated and well working therapy might be the only hope for people who cannot speak due to a lesion in their language region. Hence it would be crucial if a therapy like ours is to be communicated, implemented and applied by health institutions and the rehabilitation programs. For how useful is it to know that MIT works and is a great tool for helping aphasics recovering their speech if the aphasics all over the world cannot access the therapy unless they are enrolled in one of the studies? Therefore an important aspect of this kind of clinical reserach studies should be the training of people like speech language pathologists to apply the therapy, and to deliver it globally, so that the most possible amount of patients can benefit from it. However, unlike other not-language specific therapies, MIT is bound to the particular language spoken in a country and therefore to the unique and specific culture of a certain region. As a conequence the global application of MIT entails – after the translation – also the consideration and incorporation of cultural differences which are expressed in aspects of structure and use of language. Surprisingly there are already a few studies which tried ot incorporate MIT into other language systems such as Romanian (Popovici and Mihailescu, 1992), Japanese (Seki and Sugishita, 1983), or Persian

(Bonakdarpour et al., 2003). An excellent role model in the endeavour of the putting the research into practice is Michael Thaut. He not only developed simple, but very efficient tools for the recovery of motor functions in Parkinsons's, Huntington's disease and stroke (McIntosh et al., 1997; Thaut et al., 1997; Thaut et al., 1999), but he is one of the few scientists who takes the challenge to actively bring the research to the people who actually need it. He speaks at many events around the world, trying to disseminate his know-how and educate people in order to help as many people as possible with his findings. In a personal communication with him, he mentioned the need for skilled therapists. According to him, he is approached by many neurologists who would want to hire therapists with the practical knowledge and are able to use and apply these new techniques. Thus, to me Thaut's work is a beautiful example of research which is not just done for the research or the researcher's sake, but is actually used to help patients recover or at least improve their lost or impaired functions.

In the field of MIT where I have been engaged in for already more than 5 years this transfer to the practical field or an implementation into a rehabilitaion program has not taken place yet. But making this tool available for everybody would also be my dream for MIT. During my time in Boston, I have experienced a large interest in this form of therapy. Our lab got inquires from all over the world. The problem is that we do not have enough resources for actually going out to train and educate the therapists. For that to happen one would need to hire somebody who specifically connects research, national boards and institutions in order to establish a network for organization, distribution and education – a task which is time consuming, financially straining and nowadays – in times with difficult economical situations and consequently cuts in available funding for research – a mission (almost) impossible.

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9 Sarah Marchina – Curriculum Vitae

Education

2007 – 2010 *Ph.D. student of Neuropsychology,* University of Zurich (Switzerland), Faculty of Arts

Doctoral thesis defense (in fall 2010): *From singing to speaking: using Melodic Intonation Therapy to facilitate language recovery in patients with non-fluent aphasia* (magna cum laude)

Prof. Lutz Jäncke, Ph.D. (Supervisor), Prof. Martin Meyer, Ph.D. (Co-Supervisor), Department of Psychology, Chair of Neuropsychology

2006 *Master of Science (Lizentiat) in Psychology/Neuropsychology,* University of Zurich, Faculty of Arts

Master thesis: *Classical conditioning in the human auditory cortex using non-aversive stimuli: an fMRI study* (grade 5.5, i.e. very good)[21]

Prof. Lutz Jäncke, Ph.D. (Supervisor), PD Martin Meyer, Ph.D. (Co-Supervisor), Department of Psychology, Chair of Neuropsychology

1997-1998 *Student of Classical Percussion*, Lucerne University of Applied Sciences and Arts (Switzerland), Department of Music (Konservatorium), Prof. Erwin Bucher

1995 *Primary School Teacher's Diploma (Schweizerisches Primarlehrdiplom),* University of Teachers Education Central Switzerland (Kantonales Lehrerseminar), Lucerne

Scholarships

2007 – 2009 Swiss National Foundation Scholarship for prospective researchers

Research Experience

Since 04/12 *Research Fellow*, Beth Israel Deaconess Medical Center (BIDMC)/Harvard Medical School, Department of Neurology, Boston (USA), Dr. Sandeep Kumar, M.D. (Supervisor)

Since 04/07 *Research Fellow,* Music, Stroke Recovery and Neuroimaging Laboratory, BIDMC/Harvard Medical School, Department of Neurology, Boston (USA), Gottfried Schlaug, M.D., Ph.D. (Supervisor)

05/04 – 04/05 *Research Assistant and Tutor,* University of Zurich (Switzerland), Chair of Neuropsychology, Prof. Lutz Jäncke, Ph.D.

10/03 – 03/04 *Research Internship,* Music, Stroke Recovery and Neuroimaging Laboratory, BIDMC/Harvard Medical School, Department of Neurology, Boston (USA), Gottfried Schlaug, M.D., Ph.D. (Supervisor)

[21] According to the Swiss grading scheme with grades distributed from 6.0 down to 1.0

Professional Experience

12/06 – 02/07 *Associate Carer for the Elderly*, Kirchfeld - Haus für Betreuung und Pflege, Horw/LU (Switzerland)

01/05 – 12/06 *Psychological Testing Assistant*, Swiss Army Recruitment Center, Mels/GR (Switzerland), Stefan Monstein, Psychologist SBAP/BDP

08/06 – 11/06 *Clinical Postgraduate Internship*, Neurorehabiliation, Zürcher Höhenklinik, Faltigberg-Wald/ZH (Switzerland), Irving Speight, Ph.D. (Supervisor)

08/03 – 12/04 *Associate Carer for the Elderly (part-time)*, Blinden-Fürsorge Innerschweiz (Blindenheim), Horw/LU (Switzerland)

01/00 – 09/02 *Irish Dance Instructor (part-time)*, Continental Irish Dance Academy, Gery Bucher, Lucerne (Switzerland)

07/98 – 07/03 *Associate Carer for the Elderly (part-time)*, Kirchfeld - Haus für Betreuung und Pflege, Horw/LU (Switzerland)

08/97 – 06/98 *Percussion Teacher*, Public Music Schools, Neuenkirch/LU and Knutwil/LU (Switzerland)

Publications

Journal publications

Wan, C. Y., Marchina, S., Norton, A., & Schlaug, G. (2012). Atypical hemispheric asymmetry in the arcuate fasciculus of completely nonverbal children with autism. Ann NY Acad Sci, 1252(1):332-7.

Zipse, L., Norton, A., Marchina, S., & Schlaug, G. (2012). When right is all that is left: plasticity of right-hemisphere tracts in a young aphasic patient. Ann NY Acad Sci, 1252(1):237-45.

Marchina, S., Zhu, L.L., Norton, A., Zipse, L., Wan, C.Y., & Schlaug, G. (2011). Impairment of speech production predicted by lesion load of the left arcuate fasciculus. Stroke, 42:2251-56.

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Meyer, M., Baumann, S., Marchina, S., & Jancke, L. (2007). Hemodynamic responses in human multisensory and auditory association cortex to purely visual stimulation. BMC Neuroscience, 8 (14).

Book chapters

Schlaug, G., Marchina, S., & Norton, A. (2008). From singing to speaking: why patients with Broca's aphasia can sing and how that may lead to recovery of expressive language functions. Music Perception, 25:315-323.

Abstracts/Posters for Conferences

Wan, C.Y., Marchina, S., Norton, A., & Schlaug G. (2011). Functional connectivity in patients with Broca's aphasia following intensive Melodic Intonation Therapy. Human Brain Mapping, Quebec City.

Wang, J., Zhu, L., Marchina, S., Norton, A., Zuk, J., Wan, C., & Schlaug, G. (2011). Functional or structural brain imaging: Which is the better predictor of recovery from aphasia? Human Brain Mapping, Quebec City.

Zheng, X., Wan, C.Y., Marchina, S., Norton, A., & Schlaug, G. (2011). Intensive therapy induces white matter changes in stroke patients with aphasia. Human Brain Mapping, Quebec City.

Marchina, S., Zhu, L.L., Zipse, L., Norton, A., Wan, C., & Schlaug, G. (2010). Lesion load of the arcuate fasciculus predicts fluency in patients with Broca's aphasia after stroke. Oral abstract presented at The American Heart Association International Stroke Conference: San Antonio, TX.

Zipse, L., Norton, A., Marchina, S., & Schlaug, G. (2009). A New perspective on an old argument: singing versus speaking in nonfluent aphasia. Human Brain Mapping, San Francisco.

Norton, A., Marchina, S., & Schlaug, G. (2008). From singing to speaking: post-stroke language recovery through Melodic Intonation Therapy. Neurosciences and Music III, Montreal.

Marchina, S., Loui, P., Schulze K., Forgeard, M., Norton, A., & Schlaug, G. (2008). Neural correlates of amusia: Are the deficits structural or functional? Neurosciences and Music III, Montreal.

Schlaug, G., Norton, A., & Marchina, S. (2008). The role of the right hemisphere in post-stroke language recovery. International Stroke Meeting, New Orleans.

Cronin, K., Marchina, S., Overy, K., Norton, A., Winner, E., & Schlaug, G. (2004). Brain correlates in rhythmic processing differ in boys and girls. Cognitive Neuroscience Society, San Francsico, USA.

Cronin, K., Overy, K., Norton, A., Marchina, S., Winner E., & Schlaug, G. (2004). The effects of experience and brain maturity on neural correlates of music processing. Human Brain Mapping, Budapest, Hungary.